Docket/App No.: 0050.1618-001
Title: Methods for Identifying Agents Which...
Inventors: Leonard Guarente, *et al.*

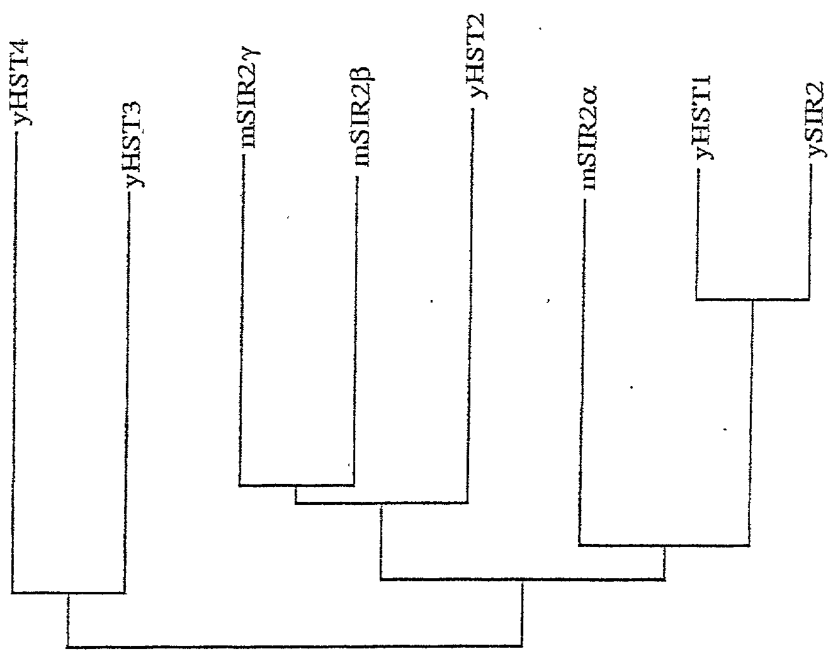

Figure 1A

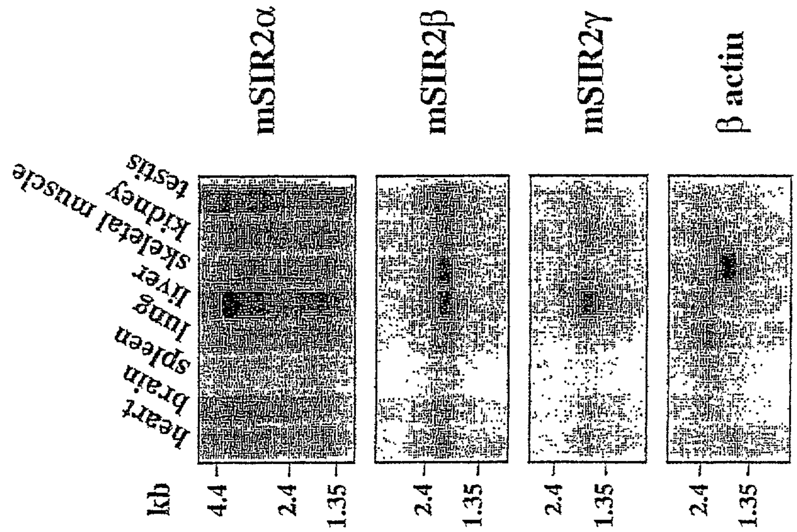

Figure 1B

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 81  ASAEREAPATAVAGDGDNGSGLRREPRAADDFDDDEGEEE
121  DEAAAAAAAAIGYRDNLLLTDGLLTNGFHSCESDDDDRT
161  SHASSSDWTPRPRIGPYTFVQQHLMIGTDPRTILKDLLPE
201  TIPPPELDDMTLWQIVINILSEPPKRKKRKDINTIEDAVK
241  LLQECKKIIVLTGAGVSVSCGIPDFRSRDGIYARLAVDFP
281  DLPDPQAMFDIEYFRKDPRPFFKFAKEIYPGQFQPSLCHK
321  FIALSDKEGKLLRNYTQNIDTLEQVAGIQRILQCHGSFAT
361  ASCLICKYKVDCEAVRGDIFNQVVPRCPRCPADEPLAIMK
401  PEIVFFGENLPEQFHRAMKYDKDEVDLLIVIGSSLKVRPV
441  ALIPSSIPHEVPQILINREPLPHLHFDVELLGDCDVIINE
481  LCHRLGGEYAKLCCNPVKLSEITEKPPRPQKELVHLSELP
521  PTPLHISEDSSSPERTVPQDSSVIATLVDQATNNNVNDLE
561  VSESSCVEEKPQEVQTSRNVENINVENPDFKAVGSSTADK
601  NERTSVAETVRKCWPNRLAKEQISKRLEGNQYLFVPPNRY
641  IFHGAEVYSDSEDDVLSSSSCGSNSDSGTCQSPSLEEPLE
681  DESEIEEFYNGLEDDTERPECAGGSGFGADGGDQEVVNEA
721  IATRQELTDVNYPSDKS
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Figure 2A

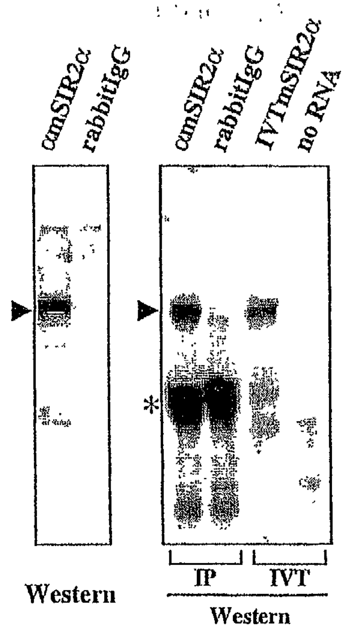


Figure 2B

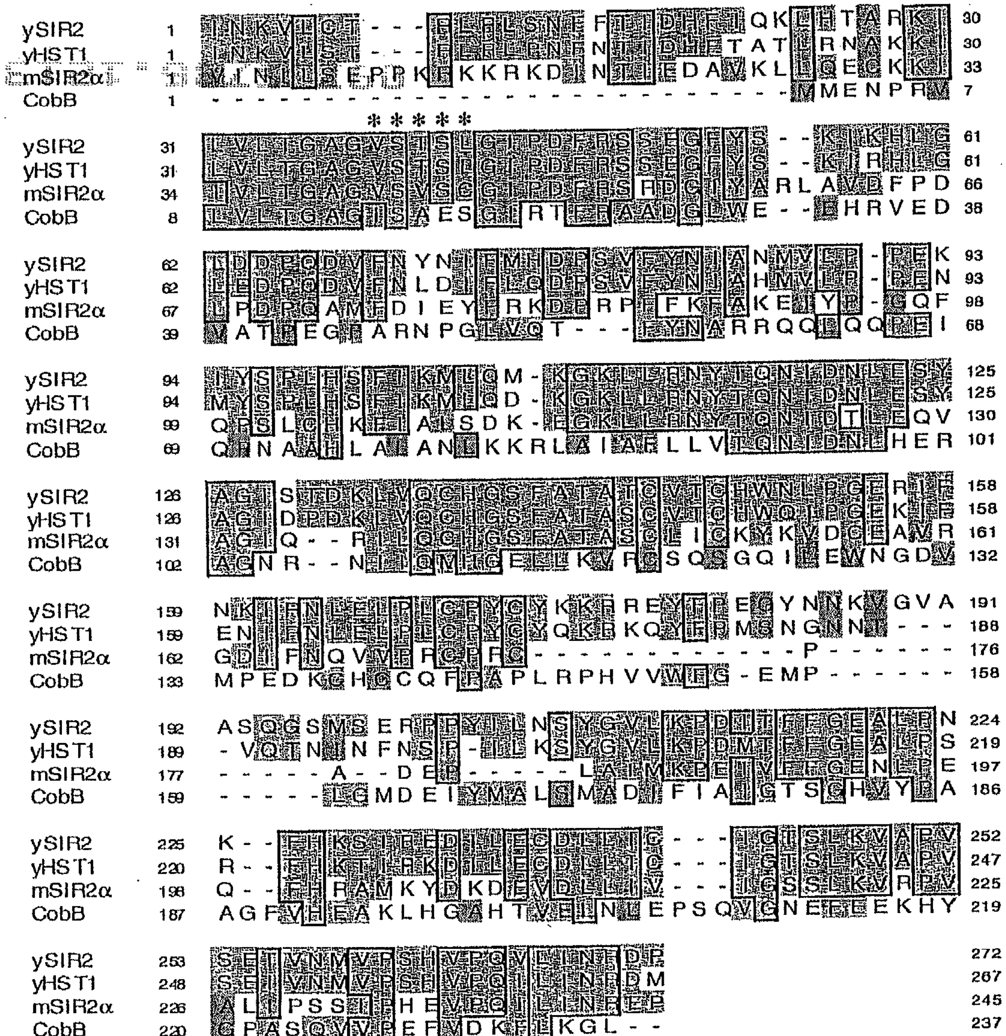


Figure 2C

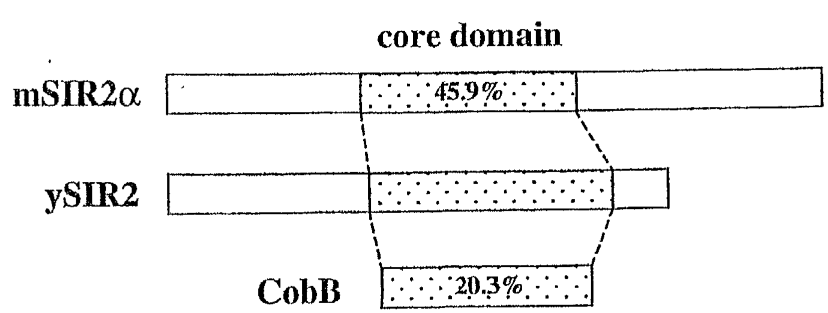


Figure 2D

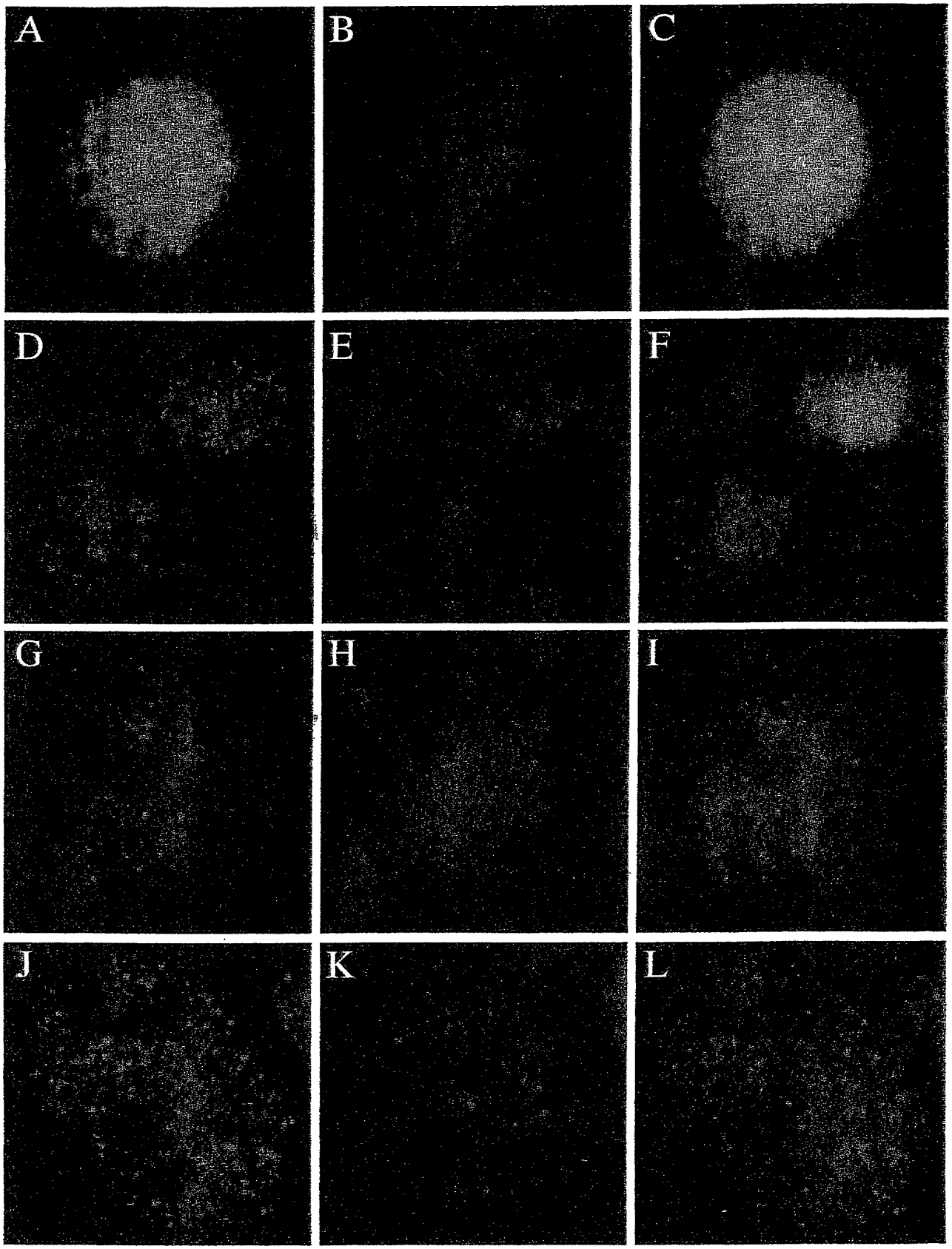

A
B
C
mSIR2α
D
E
F
mSIR2α
+
ANA-N
G
H
I
mSIR2α
+
telomere
J
K
L
mSIR2α
+
ANA-C

Figure 3

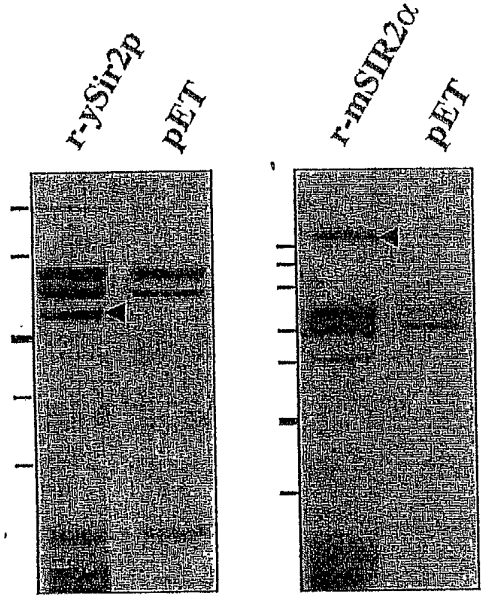
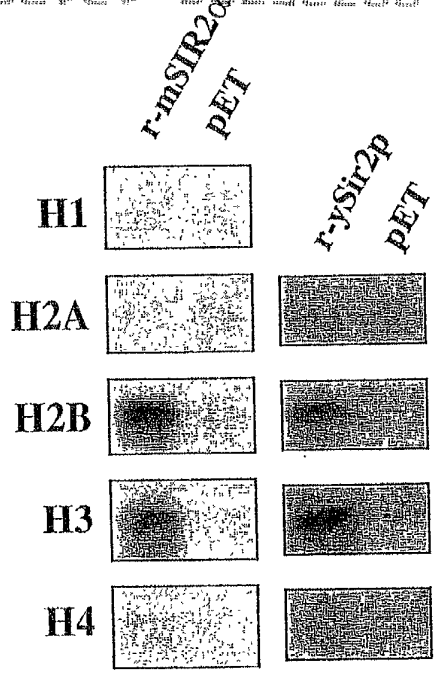


Figure 4A



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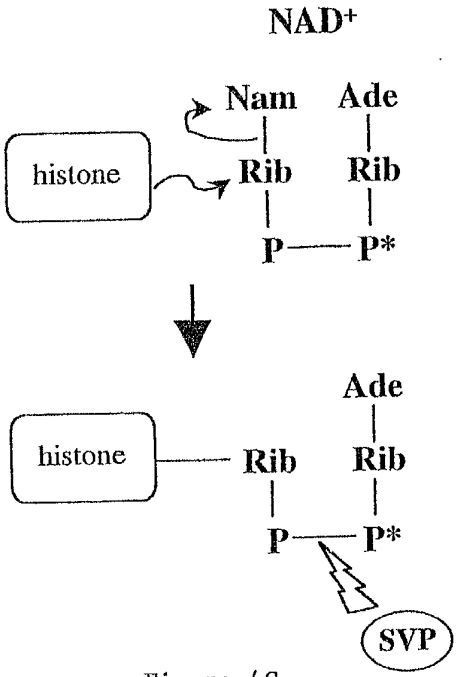

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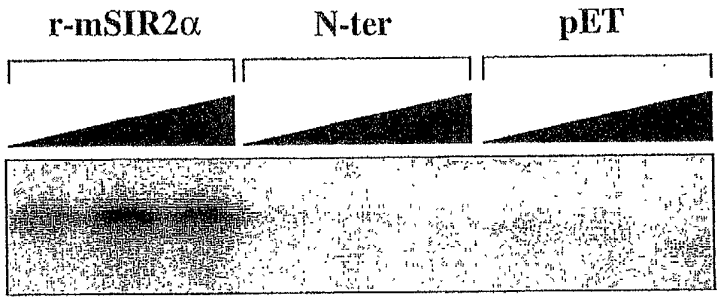
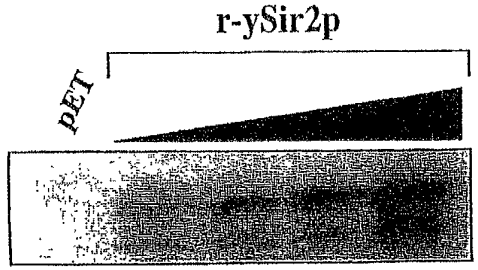


Figure 4D



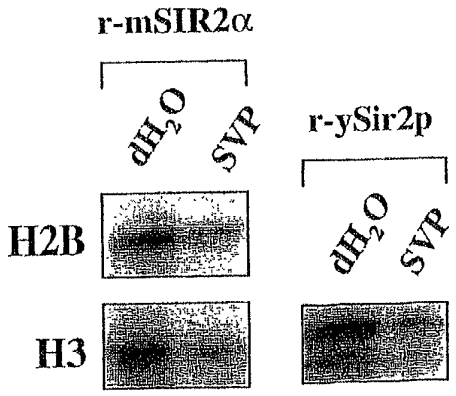


Figure 4E

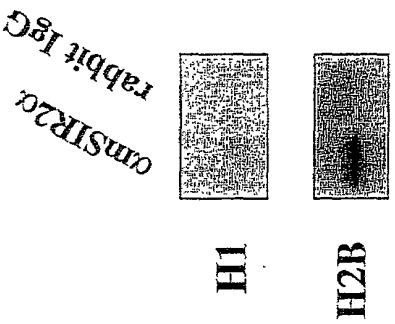


Figure 4G

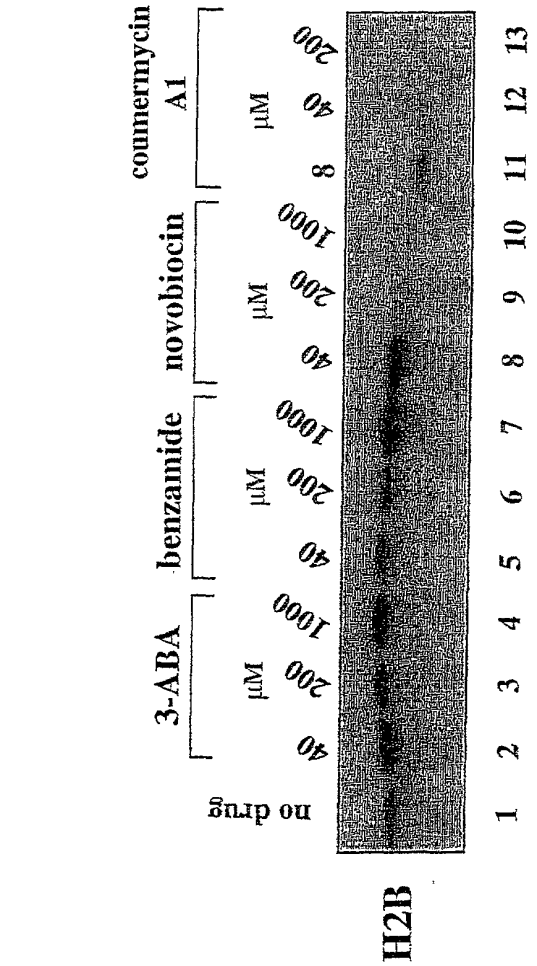


Figure 4F

H3

unAc * *
diAc ARTKQTARKSTGGKAPRKQLC

H4

* * * *
monoAc SGRGKGGKGLGKGGAKRHRC
5 8 12 16

* * * *
tetraAc AGGKGGKGMGKVGAKRHSC

Figure 5A

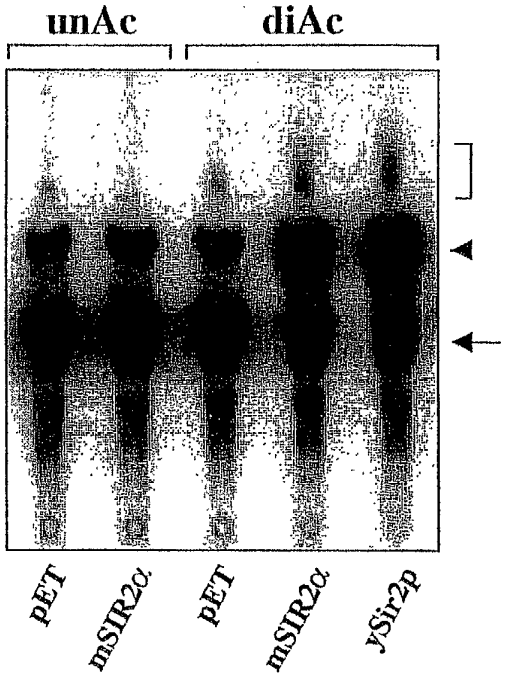


Figure 5B

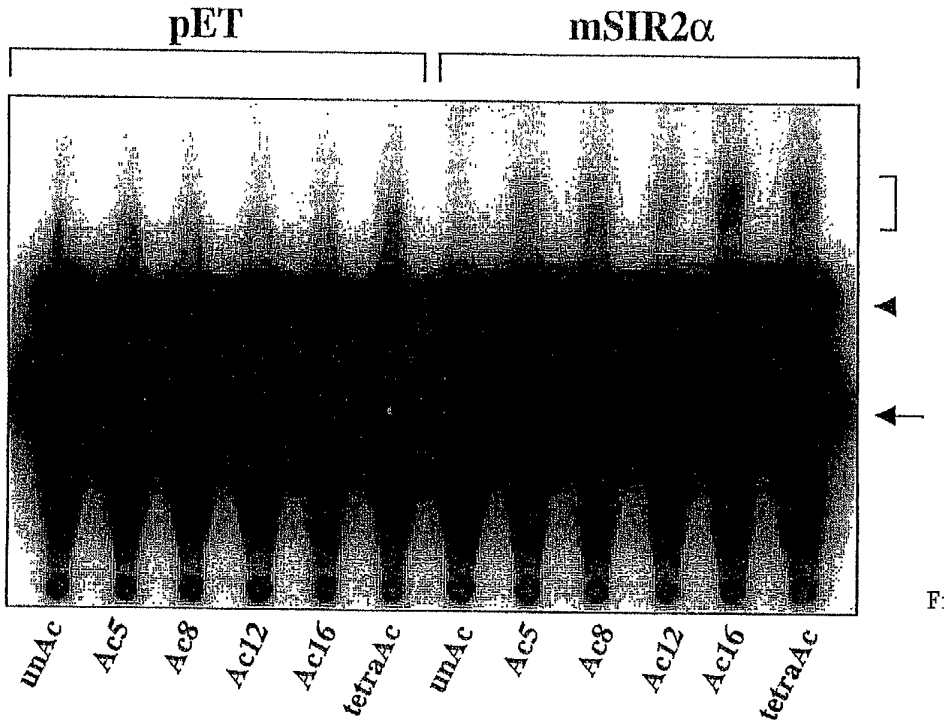


Figure 5C

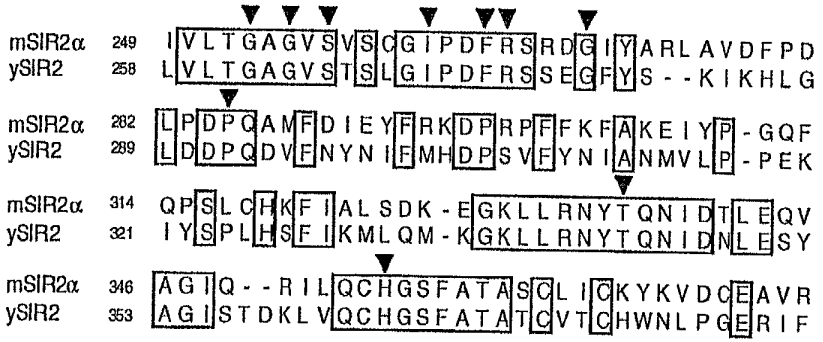


Figure 6A

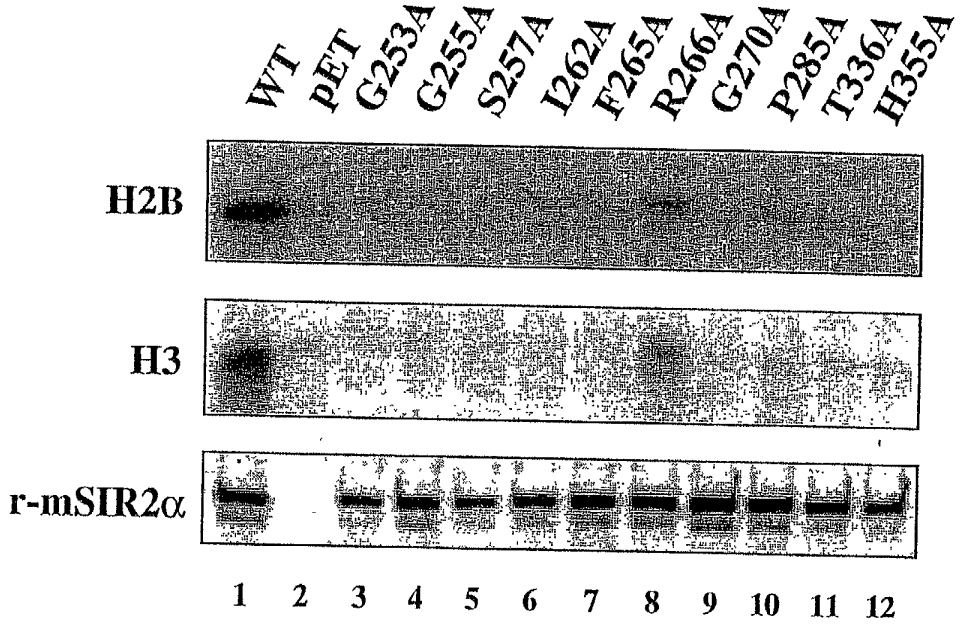


Figure 6B

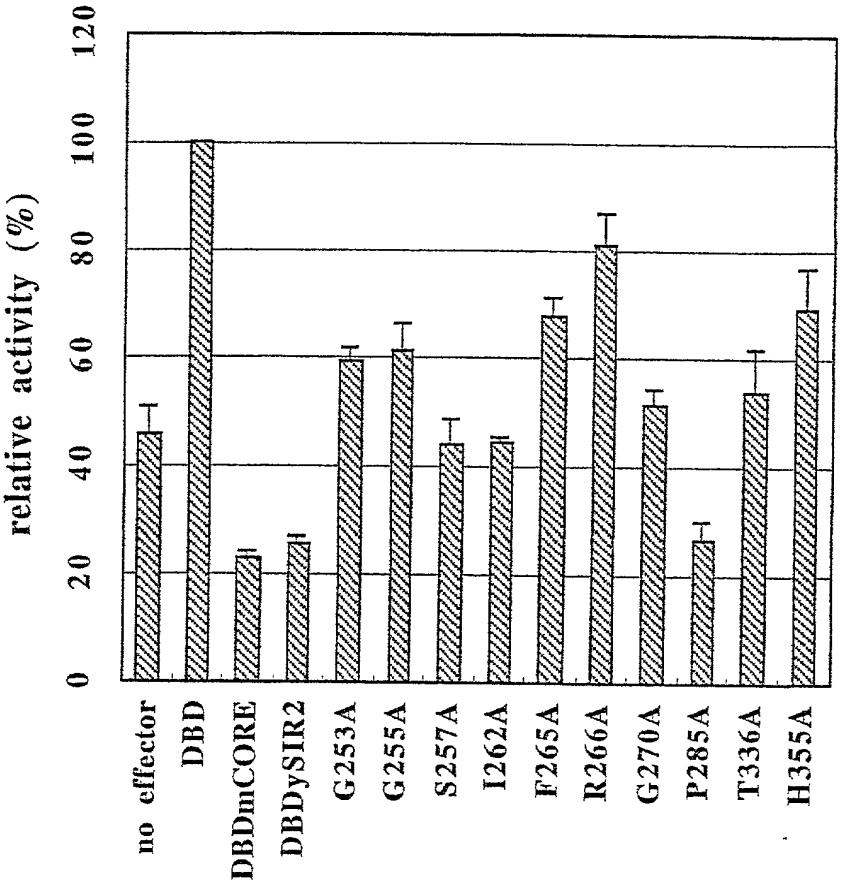


Figure 6D

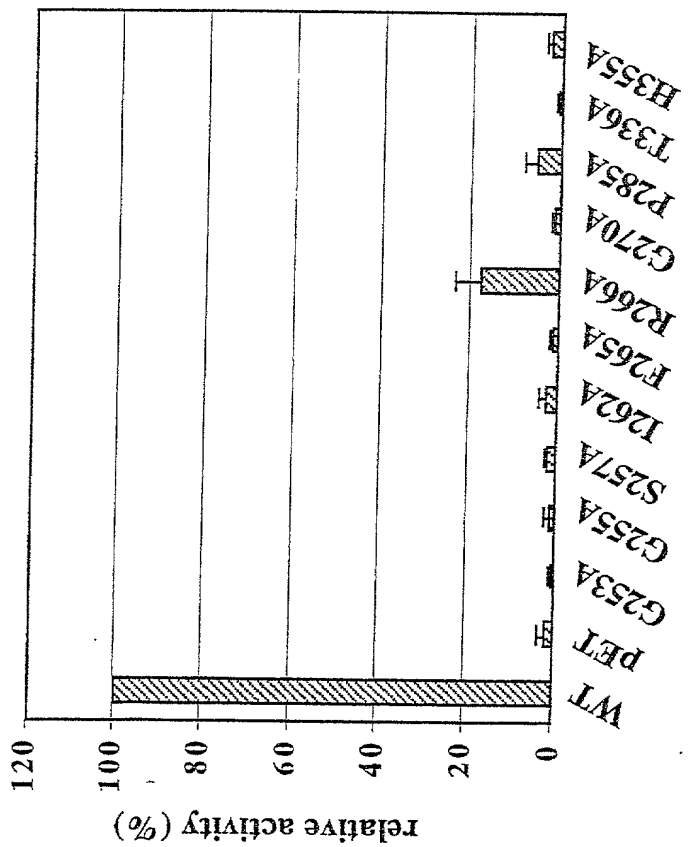


Figure 6C

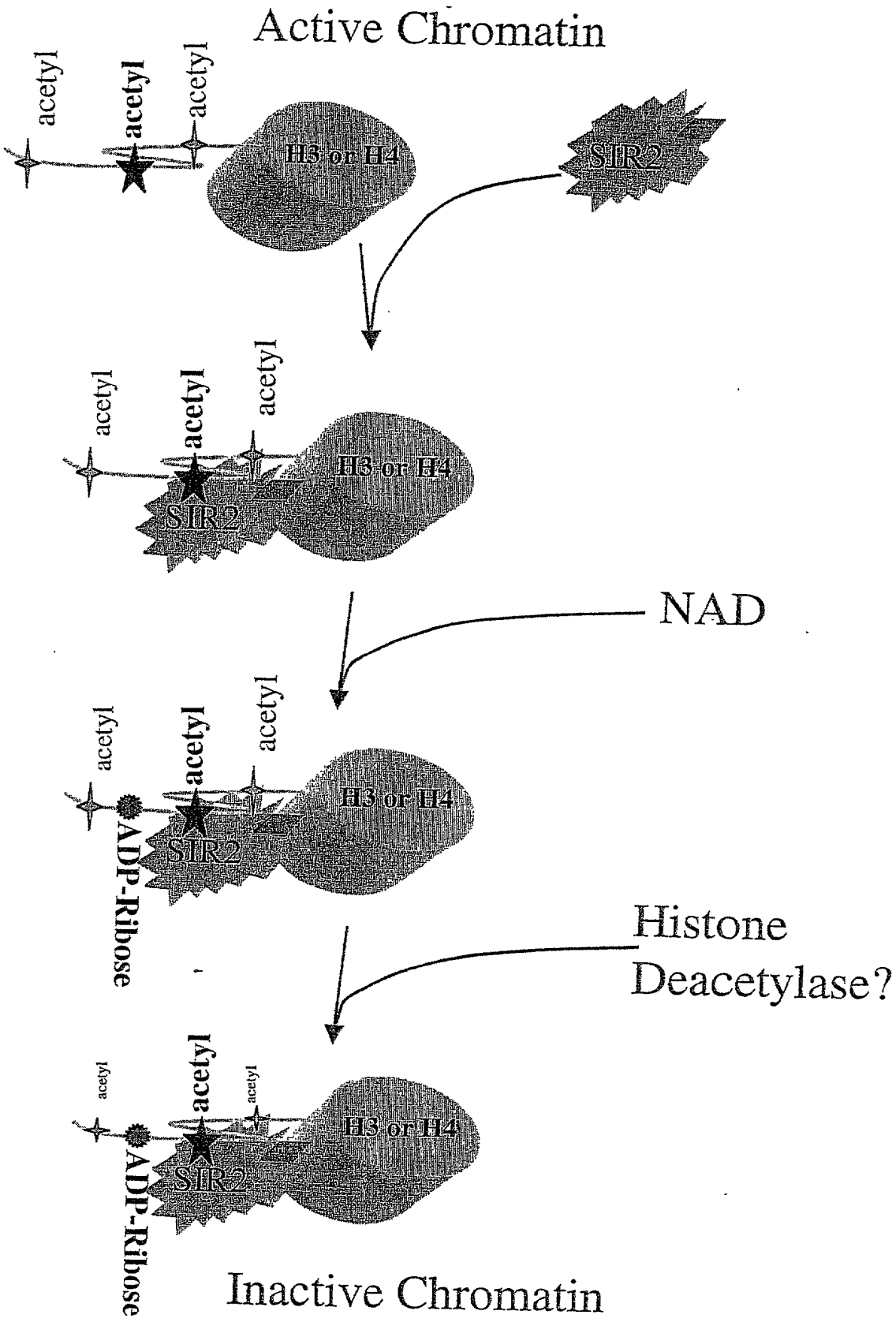

Active Chromatin
acetyl
acetyl
acetyl
H3 or H4
SIR2
acetyl
acetyl
acetyl
H3 or H4
SIR2
NAD
acetyl
acetyl
acetyl
H3 or H4
SIR2
ADP-Ribose
Histone
Deacetylase?
acetyl
acetyl
acetyl
H3 or H4
SIR2
ADP-Ribose
Inactive Chromatin

Figure 7

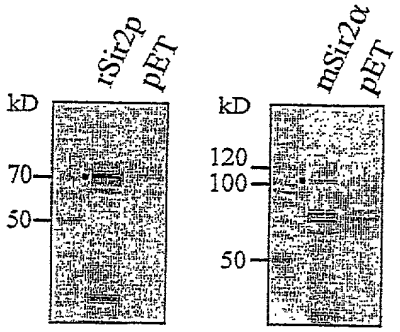


Figure 8a

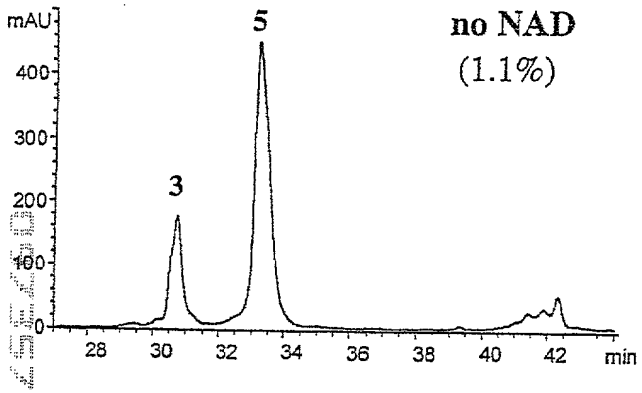


Figure 8b

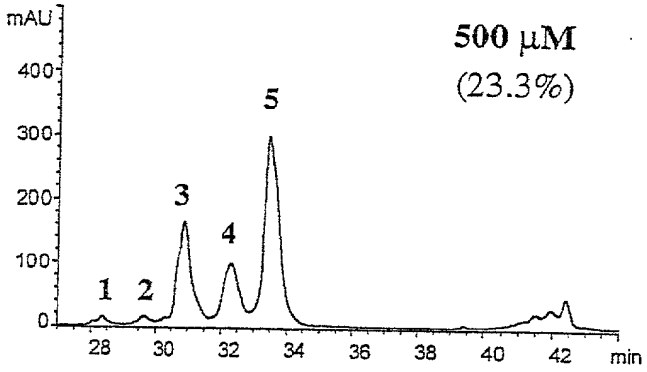


Figure 8e

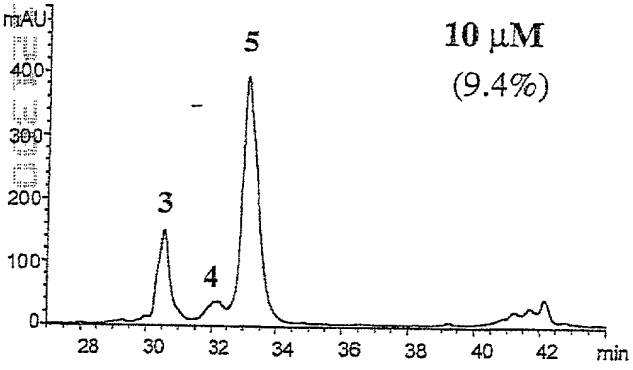


Figure 8c

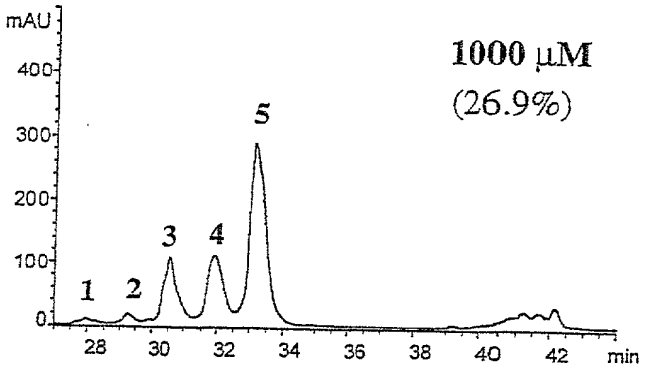


Figure 8f

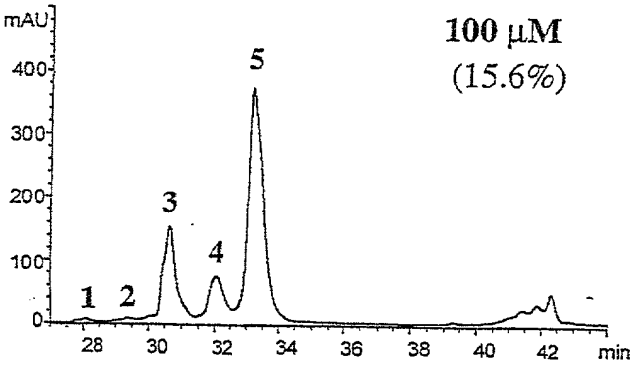


Figure 8d

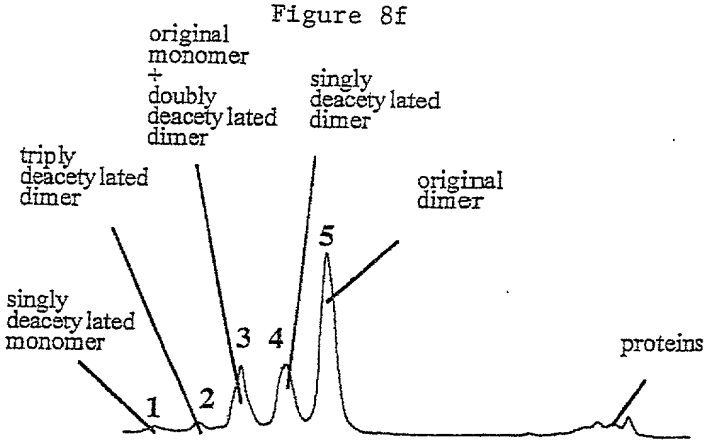


Figure 8g

Figure 9a

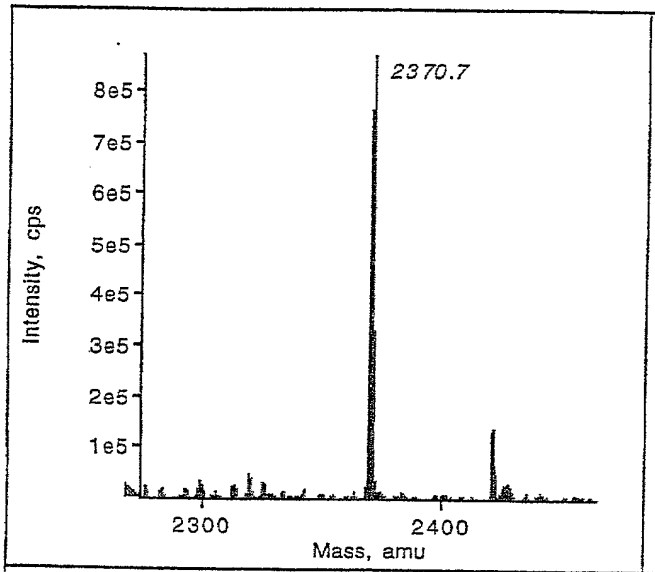
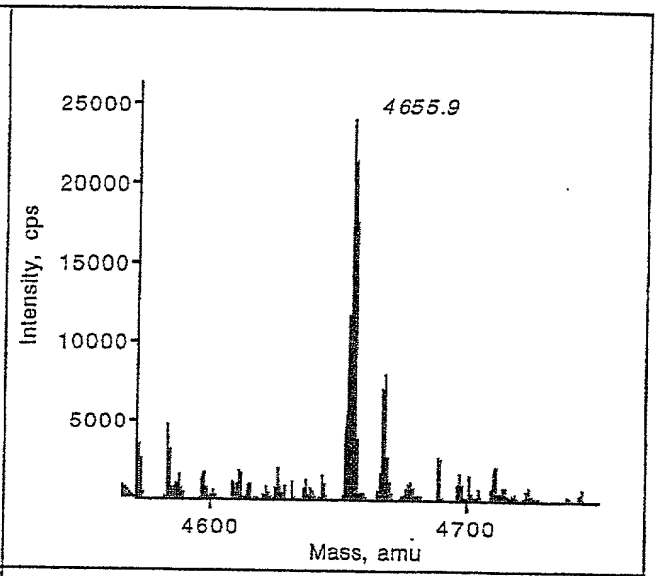


Figure 9b



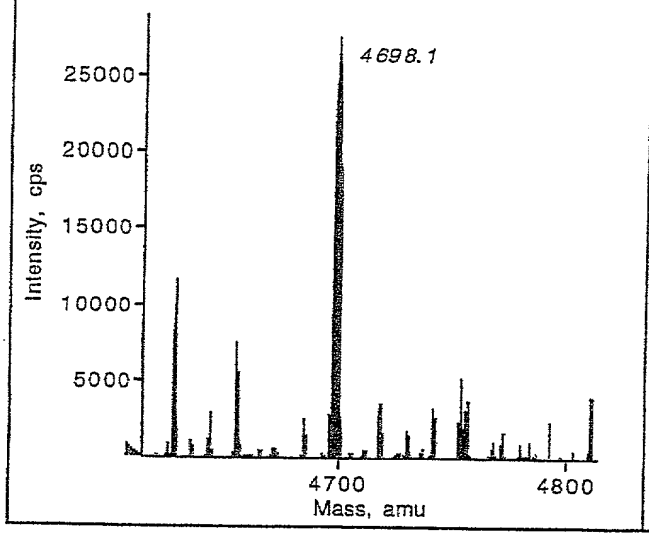


Figure 9c

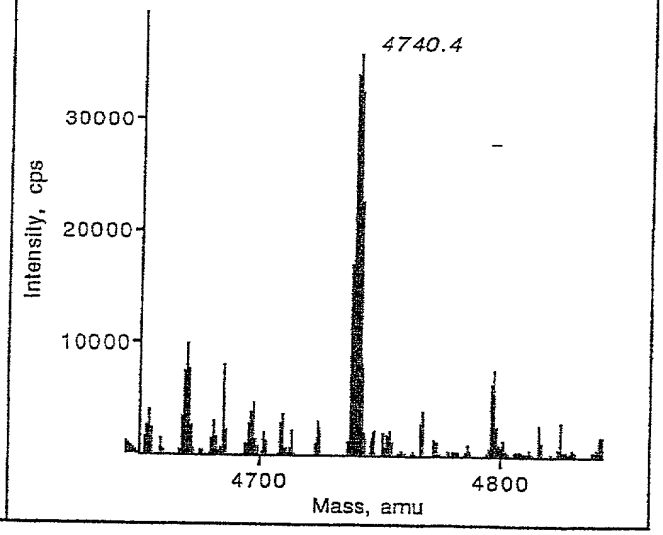


Figure 9d

peak 4

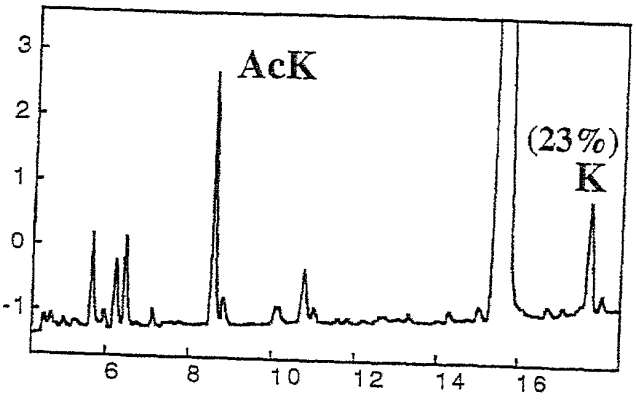


Figure 10a

peak 5

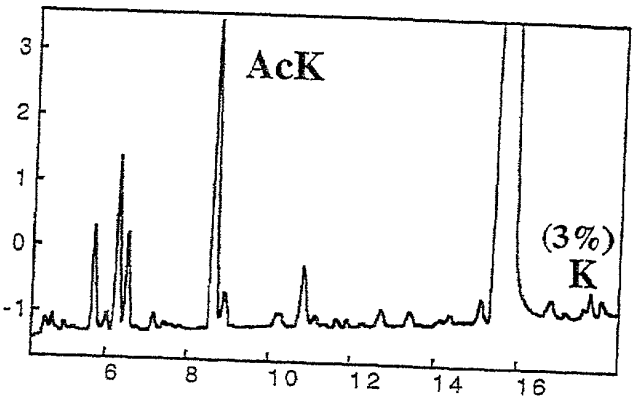


Figure 10d

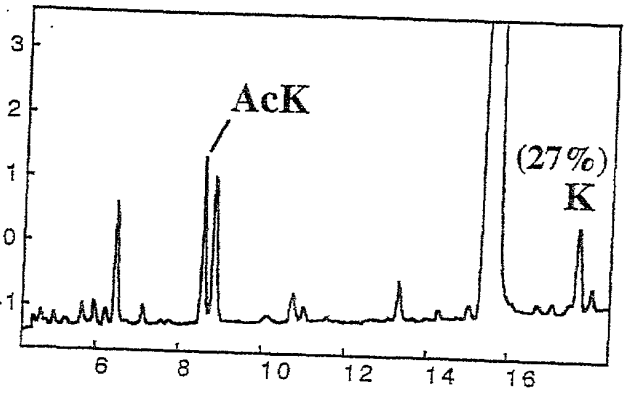


Figure 10b

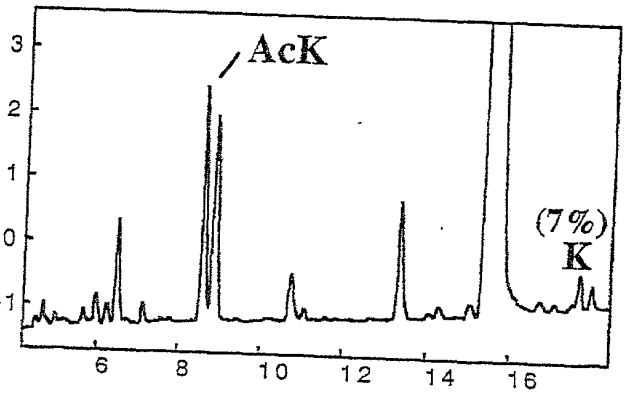


Figure 10e

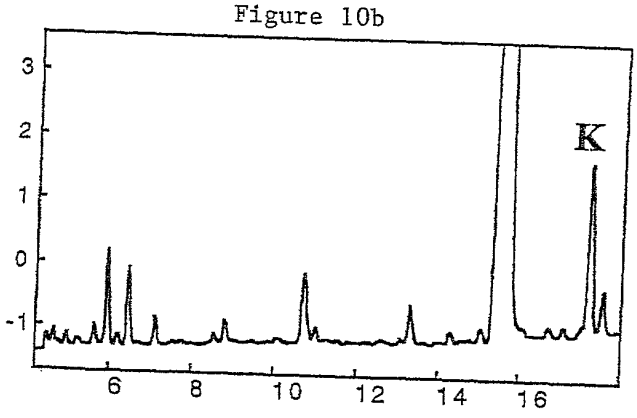


Figure 10c

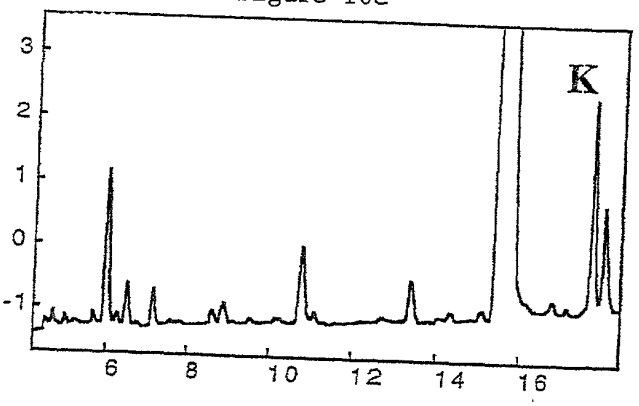


Figure 10f

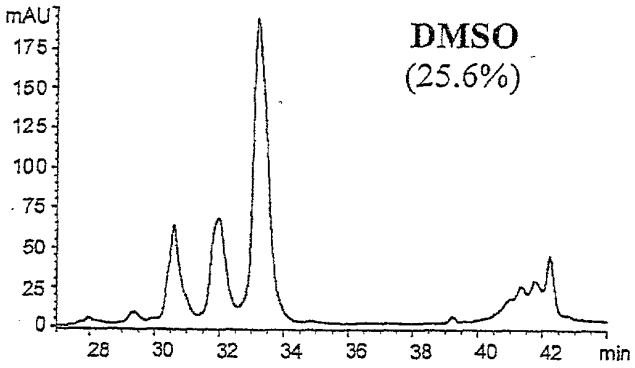


Figure 11a

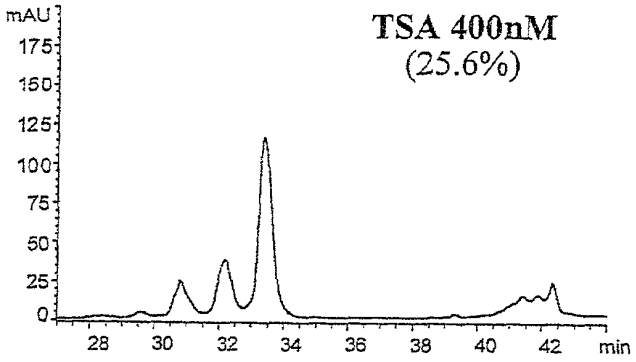


Figure 11b

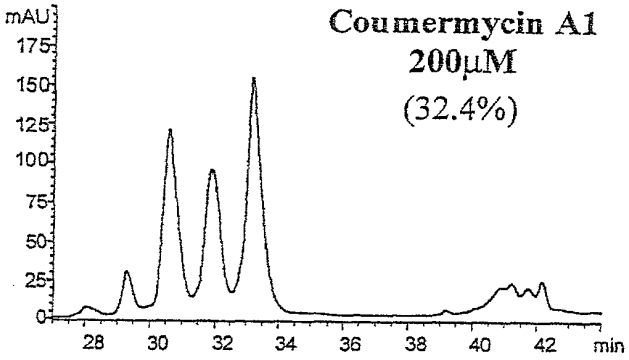


Figure 11e

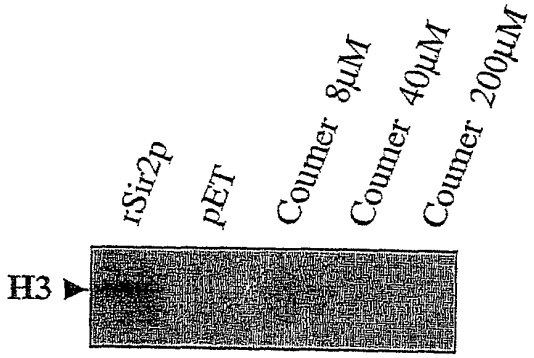


Figure 11c

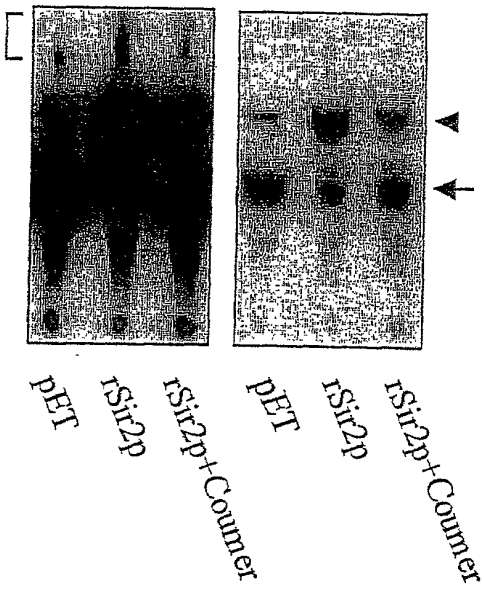


Figure 11d

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121 DEAAAAAAAAAAIGYRDNLLLTDGLLTNGFHSCESDDDDRT
161 SHASSSDWTPRPRIGPYTFVQQHLMIGTDPRTILKDLLPE
201 TIPPPELDDMTLWQIVINILSEPPKRKKRKDINTIEDAVK
241 LLQECKKIIVLTGAGVSVSCGIPDFRSRDGIYARLAVDFP
281 DLPDPQAMFDIEYFRKDPRPFFKFAKEIYPGQFQPSLCHK
321 FIALSDKEGKLLRNYTQNIDTLEQVAGIQRILQCHGSFAT
361 ASCLICKYKVDCEAVRGDIFNQVVPRCPRCPADEPLAIMK
401 PEIVFFGENLPEQFHRAMKYDKDEVDLLIVIGSSLKVRPV
441 ALIPSSIPHEVPQILINREPLPHLHFDVELLGDCDVIINE
481 LCHRLGGEYAKLCCNPVKLSEITEKPPRPQKELVHLSELP
521 PTPLHISEDSSSPERTVPQDSSVIATLVDQATNNNVNDLE
561 VSESSCVEEKPQEVQTSRNVENINVENPDFKAVGSSTADK
601 NERTSVAETVRKCWPNRLAKEQISKRLEGNQYLFVPPNRY
641 IFHGAEVYSDSEDDVLSSSSCGSNSDSGTCQSPSLEEPLE
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Figure 12a

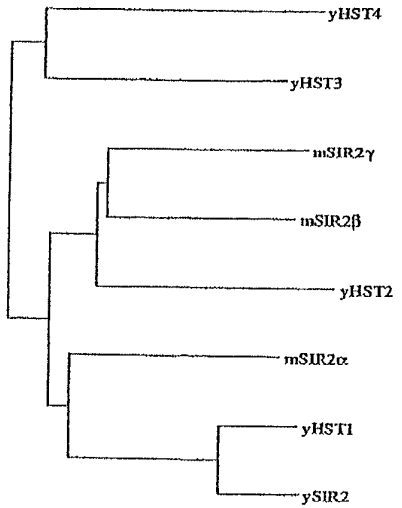

Figure 12b

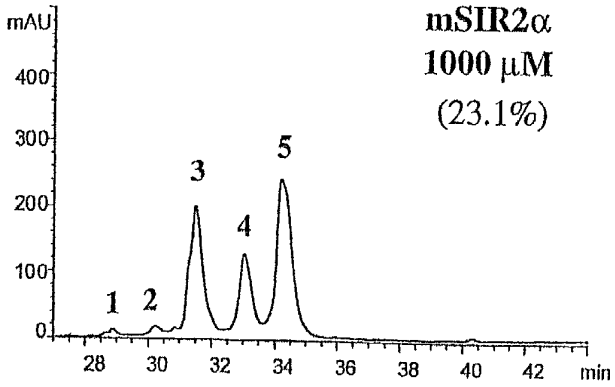

Figure 12c

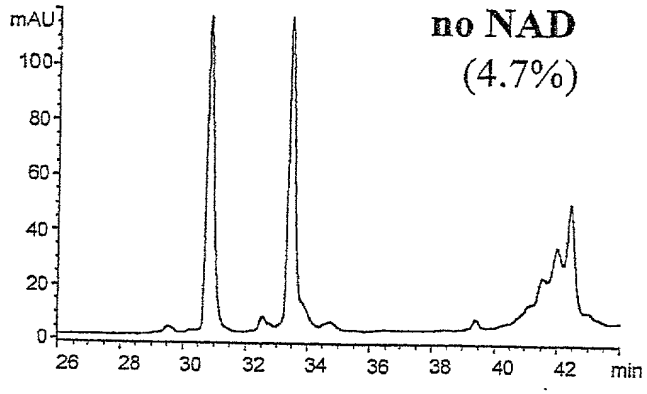

Figure 13a

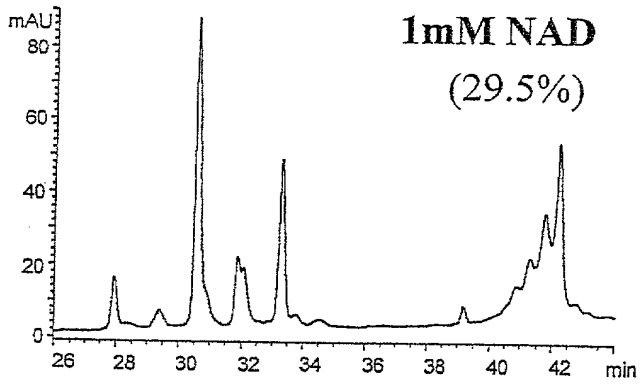

Figure 13b

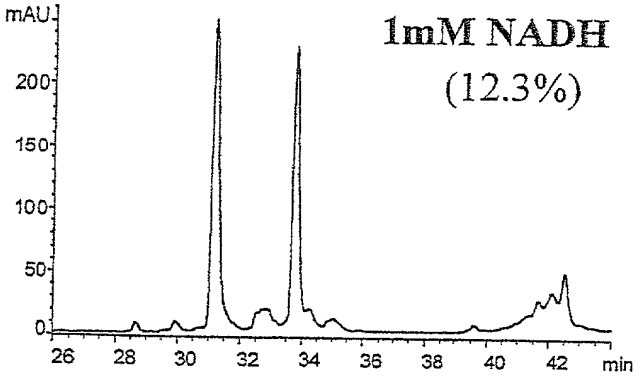

Figure 13c

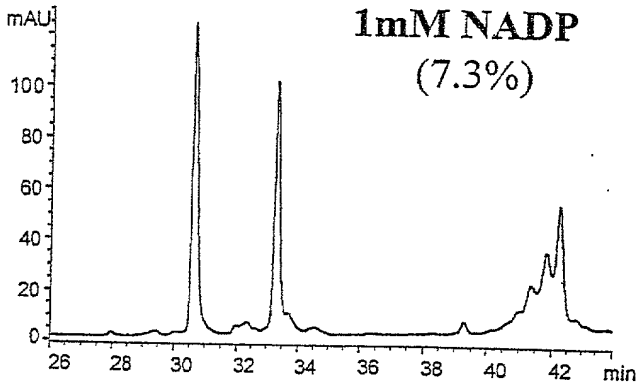

Figure 13d

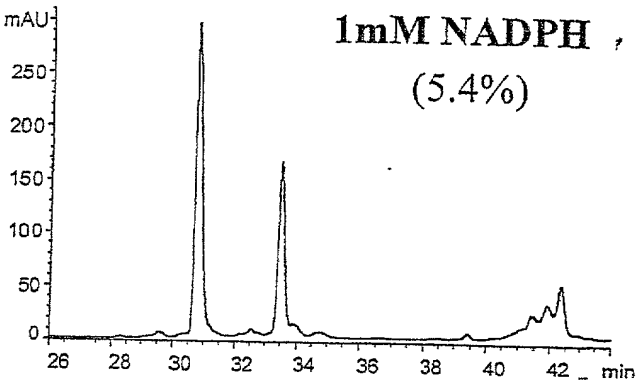

Figure 13e

Figure 14b

Figure 14c

Figure 14a

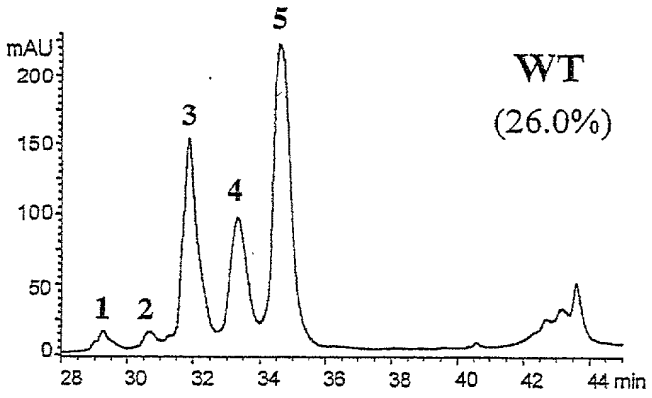

Figure 15a

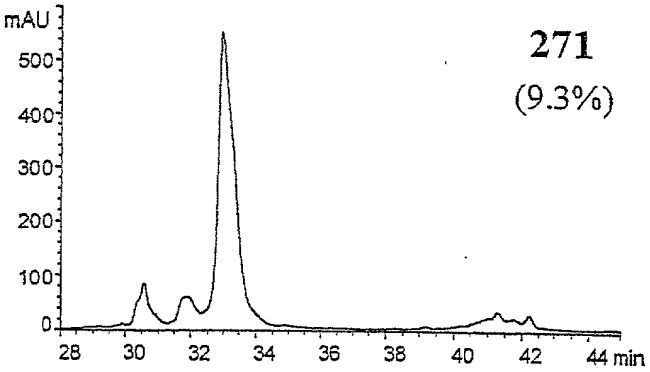

Figure 15e

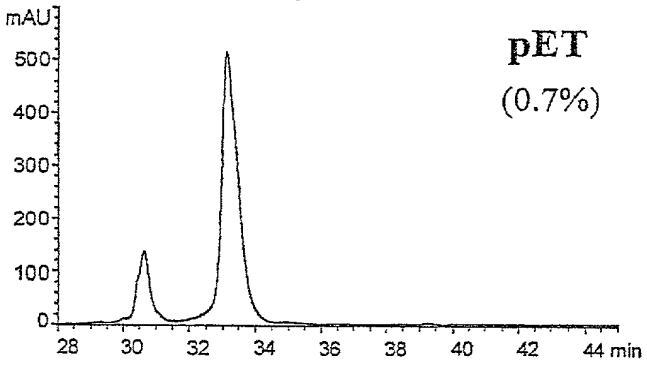

Figure 15b

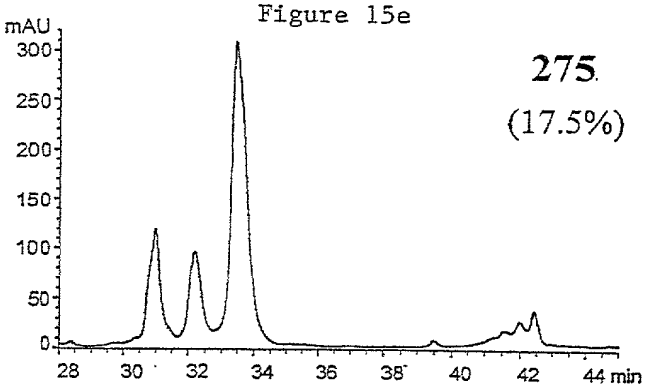

Figure 15f

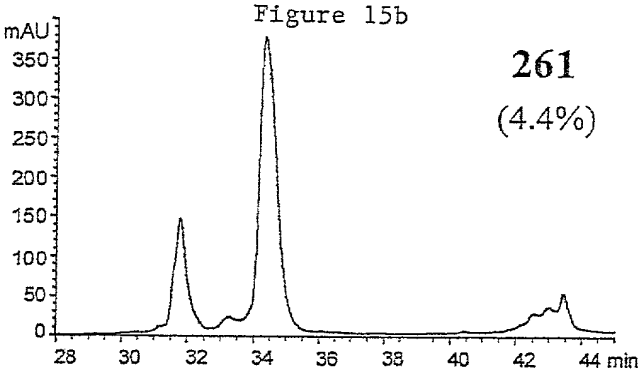

Figure 15c

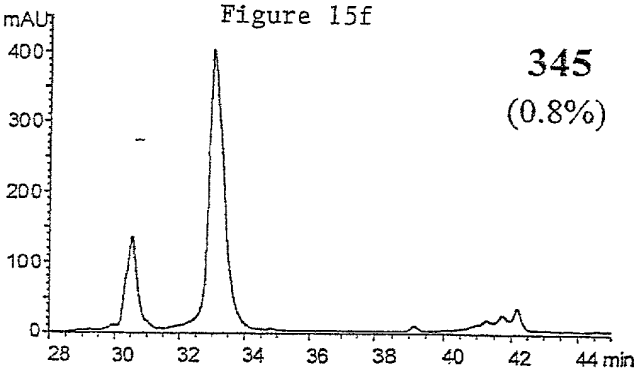

Figure 15g

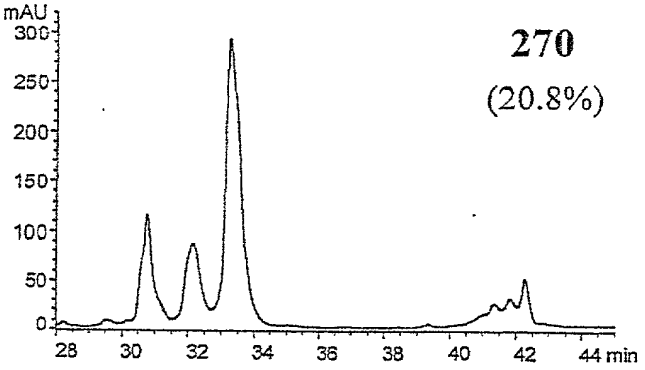

Figure 15d

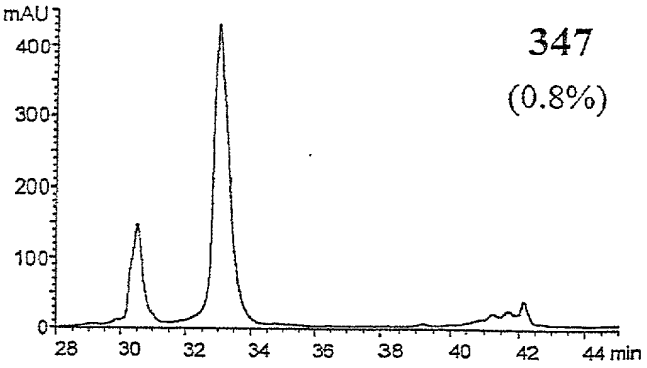

Figure 15h

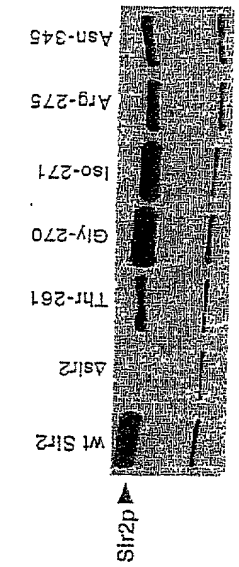

Figure 16a

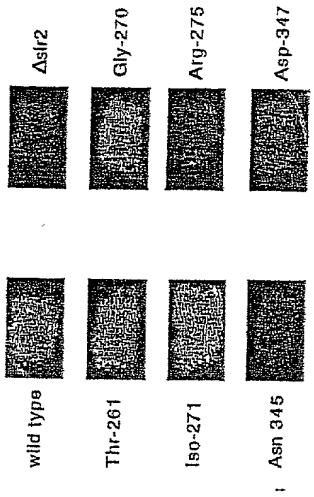

Figure 16b

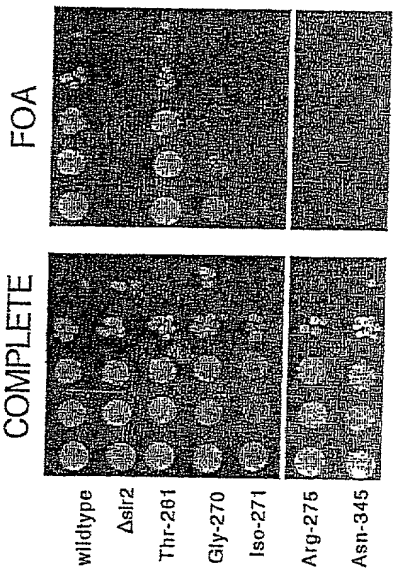

Figure 16c

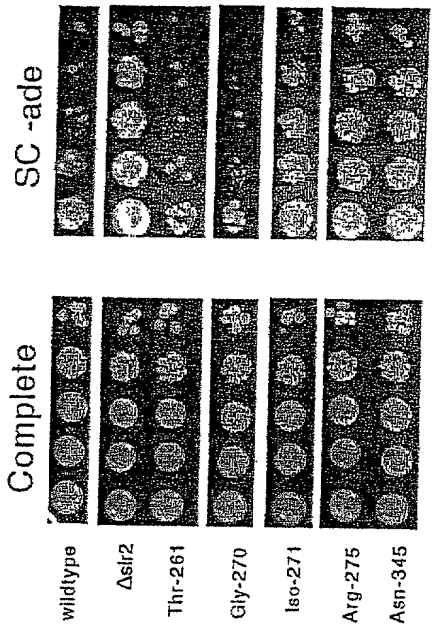

Figure 16d

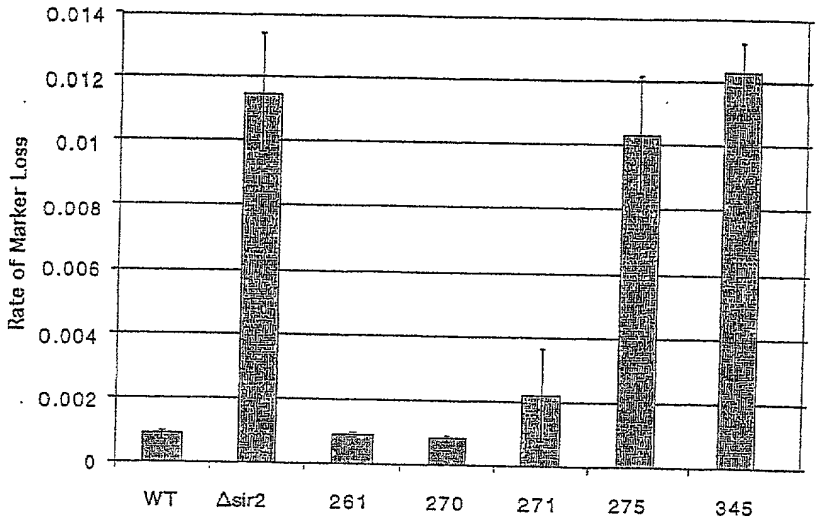

Figure 17a

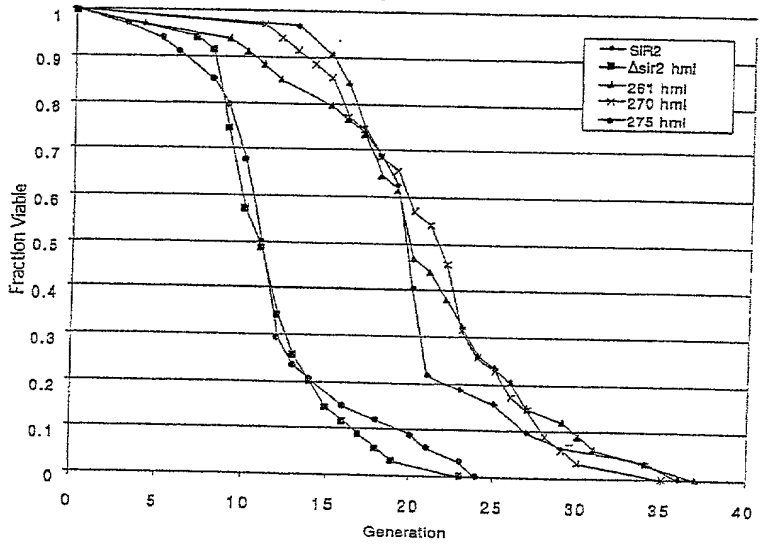

Figure 17b

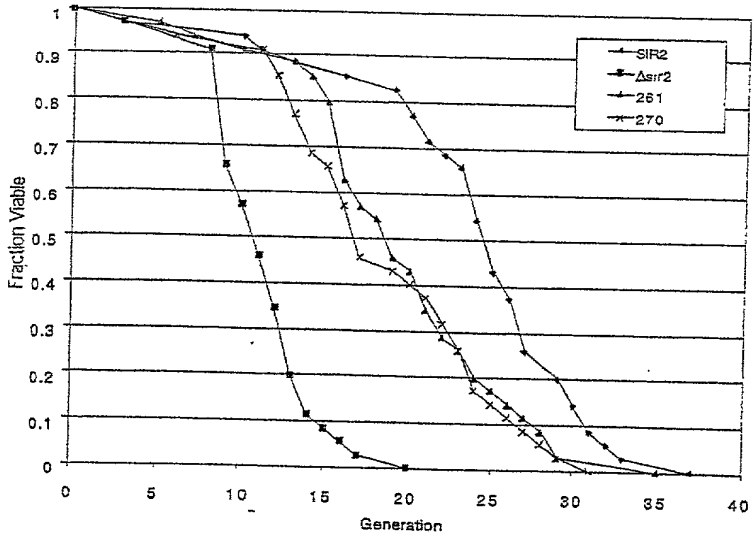

Figure 17c

Mutant	ADP-Rib. Activity (% of wt)	Deacetylase Activity (% of wt)	HM Silencing	Telomere Silencing	rDNA Silencing	rDNA Recombi-nation	Mean Life Span (HML+)
sir2Δ	0%	2.7%	-	-	-	1.15%	11.4
wildtype	100%	100%	+	+	+	0.09%	24.4
Thr-261	4%	17%	+	+	+	0.09%	19.8
Gly-270	7%	80%	+	+/-	+	0.08%	18.9
Iso-271	8%	36%	+	-	+/-	0.22%	ND
Arg-275	100%	67%	-	-	-	1.03%	ND
Asn-345	0%	3%	-	-	-	1.22%	ND
Asp-347	0%	3%	-	ND	ND	ND	ND

Figure 18

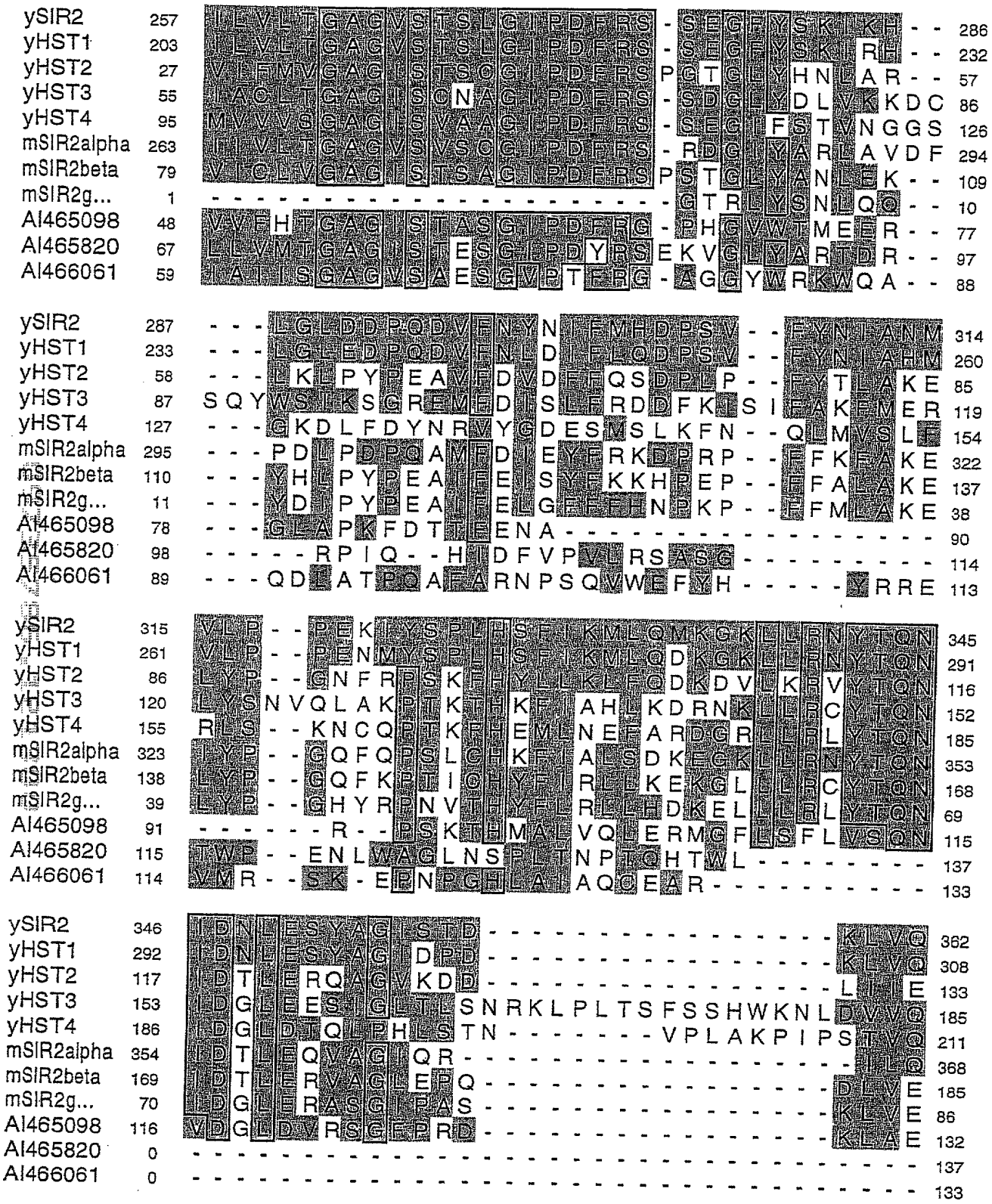
ySIR2 257 ILVLTGAGVSTSLGIPDFRS-SEGFYSKLKH-- 286
yHST1 203 JLVLTGAGVSTSLGIPDFRS-SEGFYSKLRH-- 232
yHST2 27 VLFMVGAGISTSCGIPDFRSPGTGLYHNLAR-- 57
yHST3 55 IACLTGAGISCNAGIPDFRS-SDGLYDLVKKDC 86
yHST4 95 MVVVSGAGISVAAGIPDFRS-SEGIFSTVNGGS 126
mSIR2alpha 263 IILVLTGAGVSVSCGIPDFRS-RDGIYARLAVDF 294
mSIR2beta 79 VICLVGAGISTSAGIPDFRSPSTGLYANLEK-- 109
mSIR2g... 1 ----------GTRLYSNLQQ-- 10
AI465098 48 VVFHTGAGISTASGIPDFRG-PHGVWTMEER-- 77
AI465820 67 LLVMTGAGISTESGIPDYRSEKVGLYARTDR-- 97
AI466061 59 IAIISGAGVSAESGVPTFRG-AGGYWRKWQA-- 88
ySIR2 287 ---LGLDDPQDVFNYNIFMHDPSV--EYNIANM 314
yHST1 233 ---LGLEDPQDVFNLDIFLQDPSV--FYNIAHM 260
yHST2 58 ---LKLPYPEAVFDVDFFQSDPLP--FYTLAKE 85
yHST3 87 SQYWSIKSGREMFDISLFRDDFKISIFAKFMER 119
yHST4 127 ---GKDLFDYNRVYGDESMSLKFN--QLMVSLF 154
mSIR2alpha 295 ---PDLPDPQAMFDIEYFRKDPRP--FFKFAKE 322
mSIR2beta 110 ---YHLPYPEAIFEISYFKKHPEP--FFALAKE 137
mSIR2g... 11 ---YDIPYPEAIFELGFFFHNPKP--FFMLAKE 38
AI465098 78 ---GLAPKFDTIFENA---------- 90
AI465820 98 -----RPIQ--HIDFVPVLRSASG---------- 114
AI466061 89 ---QDLATPQAFARNPSQVWEFYH-----YRRE 113
ySIR2 315 VLP--PEKIYSPLHSFIKMLQMKGKLLFNYTQN 345
yHST1 261 VLP--PENMYSPLHSFIKMLQDKGKLLRNYTQN 291
yHST2 86 LYP--GNFRPSKFHYLLKLFQDKDVLKRVYTQN 116
yHST3 120 LYSNVQLAKPTKTHKFIAHLKDRNKLLRCYTQN 152
yHST4 155 RLS--KNCQPTKFHFEMLNEFARDGRLLRLYTQN 185
mSIR2alpha 323 IYP--GQFQPSLCHKFIALSDKECKLLRNYTQN 353
mSIR2beta 138 LYP--GQFKPTICHYFIRLLKEKGLLLRCYTQN 168
mSIR2g... 39 LYP--GHYRPNVTHYFLRLLHDKELLLRLYTQN 69
AI465098 91 -------R--PSKTHMALVQLERMGFLSFLVSQN 115
AI465820 115 TWP--ENLWAGLNSPLTNPTQHTWL---------- 137
AI466061 114 VMR--SK-EPNPGHLAIAQQEAR---------- 133
ySIR2 346 IDNLESYAGLSTD----------KLVQ 362
yHST1 292 IDNLESYAGIDPD----------KLVQ 308
yHST2 117 IDTLERQAGVKDD----------LIIE 133
yHST3 153 IDGLEESIGLTLSNRKLPLTSFSSHWKNLDVVQ 185
yHST4 186 IDGLDIQLPHLSTN-------VPLAKPIPSTVQ 211
mSIR2alpha 354 IDTLEQVAGIQR----------IILQ 368
mSIR2beta 169 IDTLERVAGLEPQ----------DLVE 185
mSIR2g... 70 LDGLERASGIPAS----------KLVE 86
AI465098 116 VDGLDVRSGFPRD----------KLAE 132
AI465820 0 ---------- 137
AI466061 0 ---------- 133

Figure 19

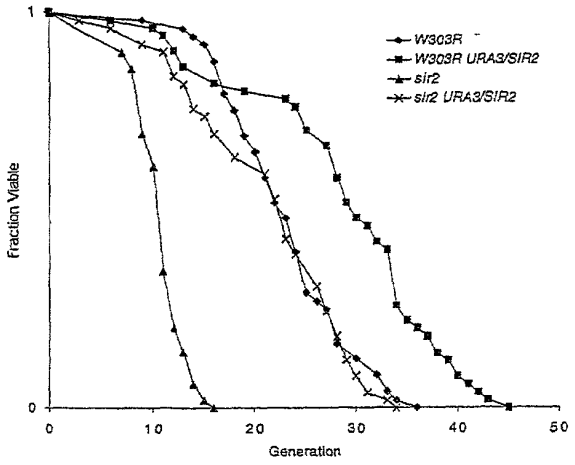
W303R
W303R URA3/SIR2
sir2
sir2 URA3/SIR2
Fraction Viable
Generation
1
0
0
10
20
30
40
50

Figure 20

```
        10         20         30         40         50         60
GCGGAGCAGAGGAGGCGAGGGCGGAGGGCCAGAGAGGCAGTTGGAAGATGGCGGACGAGG
                                                  M  A  D  E  V

        70         80         90        100        110        120
TGGCGCTCGCCCTTCAGGCCGCCGGCTCCCCTTCCGCGGCGGCCGCCATGGAGGCCGCGT
   A  L  A  L  Q  A  A  G  S  P  S  A  A  A  A  M  E  A  A  S

       130        140        150        160        170        180
CGCAGCCGGCGGACGAGCCGCTCCGCAAGAGGCCCCGCCGAGACGGGCCTGGCCTCGGGC
   Q  P  A  D  E  P  L  R  K  R  P  R  R  D  G  P  G  L  G  R

       190        200        210        220        230        240
GCAGCCCGGGCGAGCCGAGCGCAGCAGTGGCGCCGGCGGCCGCGGGGTGTGAGGCGGCGA
   S  P  G  E  P  S  A  A  V  A  P  A  A  A  G  C  E  A  A  S

       250        260        270        280        290        300
GCGCCGCGGCCCCGGCGGCGCTGTGGCGGGAGGCGGCAGGGGCGGCGGCGAGCGCGGAGC
   A  A  A  P  A  A  L  W  R  E  A  A  G  A  A  A  S  A  E  R

       310        320        330        340        350        360
CGGAGGCCCCGGCGACGGCCGTGGCCGGGGACGGAGACAATGGGTCCGGCCTGCGGCGGG
   E  A  P  A  T  A  V  A  G  D  G  D  N  G  S  G  L  R  R  E

       370        380        390        400        410        420
AGCCGAGGGCGGCTGACGACTTCGACGACGACGAGGGCGAGGAGGAGGACGAGGCGGCGG
   P  R  A  A  D  D  F  D  D  D  E  G  E  E  E  D  E  A  A  A

       430        440        450        460        470        480
CGGCAGCGGCGGCGGCAGCGATCGGCTACCGAGACAACCTCCTGTTGACCGATGGACTCC
   A  A  A  A  A  A  I  G  Y  R  D  N  L  L  L  T  D  G  L  L

       490        500        510        520        530        540
TCACTAATGGCTTTCATTCCTGTGAAAGTGATGACGATGACAGAACGTCACACGCCAGCT
   T  N  G  F  H  S  C  E  S  D  D  D  D  R  T  S  H  A  S  S

       550        560        570        580        590        600
CTAGTGACTGGACTCCGCGGCCGCGGATAGGTCCATATACTTTTGTTCAGCAACATCTCA
   S  D  W  T  P  R  P  R  I  G  P  Y  T  F  V  Q  Q  H  L  M

       610        620        630        640        650        660
TGATTGGCACCGATCCTCGAACAATTCTTAAAGATTTATTACCAGAAACAATTCCTCCAC
   I  G  T  D  P  R  T  I  L  K  D  L  L  P  E  T  I  P  P  P

       670        680        690        700        710        720
CTGAGCTGGATGATATGACGCTGTGGCAGATTGTTATTAATATCCTTTCAGAACCACCAA
   E  L  D  D  M  T  L  W  Q  I  V  I  N  I  L  S  E  P  P  K

       730        740        750        760        770        780
AGCGGAAAAAAAGAAAAGATATCAATACAATTGAAGATGCTGTGAAGTTACTGCAGGAGT
   R  K  K  R  K  D  I  N  T  I  E  D  A  V  K  L  L  Q  E  C

       790        800        810        820        830        840
GTAAAAAGATAATAGTTCTGACTGGAGCTGGGGTTTCTGTCTCCTGTGGGATTCCTGACT
   K  K  I  I  V  L  T  G  A  G  V  S  V  S  C  G  I  P  D  F

       850        860        870        880        890        900
TCAGATCAAGAGACGGTATCTATGCTCGCCTTGCGGTGGACTTCCCAGACCTCCCAGACC
   R  S  R  D  G  I  Y  A  R  L  A  V  D  F  P  D  L  P  D  P
```

Figure 21 a

```
      910       920       930       940       950       960
CTCAAGCCATGTTTGATATTGAGTATTTTAGAAAAGACCCAAGACCATTCTTCAAGTTTG
   Q  A  M  F  D  I  E  Y  F  R  K  D  P  R  P  F  F  K  F  A

      970       980       990      1000      1010      1020
CAAAGGAAATATATCCCGGACAGTTCCAGCCGTCTCTGTGTCACAAATTCATAGCTTTGT
   K  E  I  Y  P  G  Q  F  Q  P  S  L  C  H  K  F  I  A  L  S

     1030      1040      1050      1060      1070      1080
CAGATAAGGAAGGAAAACTACTTCGAAATTATACTCAAAATATAGATACCTTGGAGCAGG
   D  K  E  G  K  L  L  R  N  Y  T  Q  N  I  D  T  L  E  Q  V

     1090      1100      1110      1120      1130      1140
TTGCAGGAATCCAAAGGATCCTTCAGTGTCATGGTTCCTTTGCAACAGCATCTTGCCTGA
   A  G  I  Q  R  I  L  Q  C  H  G  S  F  A  T  A  S  C  L  I

     1150      1160      1170      1180      1190      1200
TTTGTAAATACAAAGTTGATTGTGAAGCTGTTCGTGGAGACATTTTTAATCAGGTAGTTC
   C  K  Y  K  V  D  C  E  A  V  R  G  D  I  F  N  Q  V  V  P

     1210      1220      1230      1240      1250      1260
CTCGGTGCCCTAGGTGCCCAGCTGATGAGCCACTTGCCATCATGAAGCCAGAGATTGTCT
   R  C  P  R  C  P  A  D  E  P  L  A  I  M  K  P  E  I  V  F

     1270      1280      1290      1300      1310      1320
TCTTTGGTGAAAACTTACCAGAACAGTTTCATAGAGCCATGAAGTATGACAAAGATGAAG
   F  G  E  N  L  P  E  Q  F  H  R  A  M  K  Y  D  K  D  E  V

     1330      1340      1350      1360      1370      1380
TTGACCTCCTCATTGTTATTGGATCTTCTCTGAAAGTGAGACCAGTAGCACTAATTCCAA
   D  L  L  I  V  I  G  S  S  L  K  V  R  P  V  A  L  I  P  S

     1390      1400      1410      1420      1430      1440
GTTCTATACCCCATGAAGTGCCTCAAATATTAATAAATAGGGAACCTTTGCCTCATCTAC
   S  I  P  H  E  V  P  Q  I  L  I  N  R  E  P  L  P  H  L  H

     1450      1460      1470      1480      1490      1500
ATTTTGATGTAGAGCTCCTTGGAGACTGCGATGTTATAATTAATGAGTTGTGTCATAGGC
   F  D  V  E  L  L  G  D  C  D  V  I  I  N  E  L  C  H  R  L

     1510      1520      1530      1540      1550      1560
TAGGTGGTGAATATGCCAAACTTTGTTGTAACCCTGTAAAGCTTTCAGAAATTACTGAAA
   G  G  E  Y  A  K  L  C  C  N  P  V  K  L  S  E  I  T  E  K

     1570      1580      1590      1600      1610      1620
AACCTCCACGCCCACAAAAGGAATTGGTTCATTTATCAGAGTTGCCACCAACACCTCTTC
   P  P  R  P  Q  K  E  L  V  H  L  S  E  L  P  P  T  P  L  H

     1630      1640      1650      1660      1670      1680
ATATTTCGGAAGACTCAAGTTCACCTGAAAGAACTGTACCACAAGACTCTTCTGTGATTG
   I  S  E  D  S  S  S  P  E  R  T  V  P  Q  D  S  S  V  I  A

     1690      1700      1710      1720      1730      1740
CTACACTTGTAGACCAAGCAACAAACAACAATGTTAATGATTTAGAAGTATCTGAATCAA
   T  L  V  D  Q  A  T  N  N  N  V  N  D  L  E  V  S  E  S  S

     1750      1760      1770      1780      1790      1800
GTTGTGTGGAAGAAAAACCACAAGAAGTACAGACTAGTAGGAATGTTGAGAACATTAATG
   C  V  E  E  K  P  Q  E  V  Q  T  S  R  N  V  E  N  I  N  V

     1810      1820      1830      1840      1850      1860
TGGAAAATCCAGATTTTAAGGCTGTTGGTTCCAGTACTGCAGACAAAAATGAAAGAACTT
   E  N  P  D  F  K  A  V  G  S  S  T  A  D  K  N  E  R  T  S

     1870      1880      1890      1900      1910      1920
CAGTTGCAGAAACAGTGAGAAAATGCTGGCCTAATAGACTTGCAAAGGAGCAGATTAGTA
   V  A  E  T  V  R  K  C  W  P  N  R  L  A  K  E  Q  I  S  K
```

Figure 21b

```
      1930       1940       1950       1960       1970       1980
AGCGGCTTGAGGGTAATCAATACCTGTTTGTACCACCAAATCGTTACATATTCCACGGTG
   R  L  E  G  N  Q  Y  L  F  V  P  P  N  R  Y  I  F  H  G  A

      1990       2000       2010       2020       2030       2040
CTGAGGTATACTCAGACTCTGAAGATGACGTCTTGTCCTCTAGTTCCTGTGGCAGTAACA
   E  V  Y  S  D  S  E  D  D  V  L  S  S  S  S  C  G  S  N  S

      2050       2060       2070       2080       2090       2100
GTGACAGTGGCACATGCCAGAGTCCAAGTTTAGAAGAACCCTTGGAAGATGAAAGTGAAA
   D  S  G  T  C  Q  S  P  S  L  E  E  P  L  E  D  E  S  E  I

      2110       2120       2130       2140       2150       2160
TTGAAGAATTCTACAATGGCTTGGAAGATGATACGGAGAGGCCCGAATGTGCTGGAGGAT
   E  E  F  Y  N  G  L  E  D  D  T  E  R  P  E  C  A  G  G  S

      2170       2180       2190       2200       2210       2220
CTGGATTTGGAGCTGATGGAGGGGATCAAGAGGTTGTTAATGAAGCTATAGCTACAAGAC
   G  F  G  A  D  G  G  D  Q  E  V  V  N  E  A  I  A  T  R  Q

      2230       2240       2250       2260       2270       2280
AGGAATTGACAGATGTAAACTATCCATCAGACAAATCATAACACTATTGAAGCTGTCCGG
   E  L  T  D  V  N  Y  P  S  D  K  S  *

      2290       2300       2310       2320       2330       2340
ATTCAGGAATTGCTCCACCAGCATTGGGAACTTTAGCATGTCAAAAAAATGAATGTTTAC

      2350       2360       2370       2380       2390       2400
TTGTGAACTTGAACAAGGAAATCTGAAAGATGTATTATTTATAGACTGGAAAATAGATTG

      2410       2420       2430       2440       2450       2460
TCTTCTTGGATAATTTCTAAAGTTCCATCATTTCTGTTTGTACTTGTACATTCAACACTG

      2470       2480       2490       2500       2510       2520
TTGGTTGACTTCATCTTCCTTTCAAGGTTCATTTGTATGATACATTCGTATGTATGTATA

      2530       2540       2550       2560       2570       2580
ATTTTGTTTTTTGCCTAATGAGTTTCAACCTTTTAAAGTTTTCAAAAGCCATTGGAATGT

      2590       2600       2610       2620       2630       2640
TAATGTAAAGGGAACAGCTTATCTAGACCAAAGAATGGTATTTCACACTTTTTTGTTTGT

      2650       2660       2670       2680       2690       2700
AACATTGAATAGTTTAAAGCCCTCAATTTCTGTTCTGCTGAACTTTTATTTTTAGGACAG

      2710       2720       2730       2740       2750       2760
TTAACTTTTTAAACACTGGCATTTTCCAAAACTTGTGGCAGCTAACTTTTTAAAATCACA

      2770       2780       2790       2800       2810       2820
GATGACTTGTAATGTGAGGAGTCAGCACCGTGTCTGGAGCACTCAAAACTTGGGCTCAGT

      2830       2840       2850       2860       2870       2880
GTGTGAAGCGTACTTACTGCATCGTTTTTGTACTTGCTGCAGACGTGGTAATGTCCAAAC

      2890       2900       2910       2920       2930       2940
AGGCCCCTGAGACTAATCTGATAAATGATTTGGAAATGTGTTTCAGTTGTTCTAGAAACA

      2950       2960       2970       2980       2990       3000
ATAGTGCCTGTCTATATAGGTCCCCTTAGTTTGAATATTTGCCATTGTTTAATTAAATAC

      3010       3020       3030       3040       3050       3060
CTATCACTGTGGTAGAGCCTGCATAGATCTTCACCACAAATACTGCCAAGATGTGAATAT

      3070       3080       3090       3100       3110       3120
GCAAAGCCTTTCTGAATCTAATAATGGTACTTCTACTGGGGAGAGTGTAATATTTTGGAC

      3130       3140       3150       3160       3170       3180
TGCTGTTTTTCCATTAATGAGGAAAGCAATAGGCCTCTTAATTAAAGTCCCAAAGTCATA
```

Figure 21c

```
      3190       3200       3210       3220       3230       3240
AGATAAATTGTAGCTCAACCAGAAAGTACACTGTTGCCTGTTGAGGATTTGGTGTAATGT

      3250       3260       3270       3280       3290       3300
ATCCCAAGGTGTTAGCCTTGTATTATGGAGATGAATACAGATCCAATAGTCAAATGAAAC

      3310       3320       3330       3340       3350       3360
TAGTTCTTAGTTATTTAAAAGCTTAGCTTGCCTTAAAACTAGGGATCAATTTTCTCAACT

      3370       3380       3390       3400       3410       3420
GCAGAAACTTTTAGCCTTTCAAACAGTTCACACCTCAGAAAGTCAGTATTTATTTTACAG

      3430       3440       3450       3460       3470       3480
ACTTCTTTGGAACATTGCCCCCAAATTTAAATATTCATGTGGGTTTAGTATTTATTACAA

      3490       3500       3510       3520       3530       3540
AAAAATGATTTGAAATATAGCTGTTCTTTATGCATAAAATACCCAGTTAGGACCATTACT

      3550       3560       3570       3580       3590       3600
GCCAGAGGAGAAAAGTATTAAGTAGCTCATTTCCCTACCTAAAAGATAACTGAATTTATT

      3610       3620       3630       3640       3650       3660
TGGCTACACTAAAGAATGCAGTATATTTAGTTTTCCATTTGCATGATGTGTTTGTGCTAT

      3670       3680       3690       3700       3710       3720
AGACAATATTTTAAATTGAAAAATTTGTTTTAAATTATTTTTACAGTGAAGACTGTTTTC

      3730       3740       3750       3760       3770       3780
AGCTCTTTTTATATTGTACATAGACTTTTATGTAATCTGGCATATGTTTTGTAGACCGTT

      3790       3800       3810       3820       3830       3840
TAATGACTGGATTATCTTCCTCCAACTTTTGAAATACAAAAACAGTGTTTTATACTAAAA

      3850       3860       3870
AAAAAAAAAGTCGACGCGGCCGCGAATTC
```

Figure 21d

```
        10         20         30         40         50         60
CCACGCGTCCGCGGACGCGTGGGCACGGGACAGAGCAGTCGGTGACAGTCCCGAGGGCCC
   T  R  P  R  T  R  G  H  G  T  E  Q  S  V  T  V  P  R  A  P

        70         80         90        100        110        120
CCACCCCGTTCCCATGGCCGAGCCGGACCGATTCAGACTCGGACACTGAGGGAGGAGCCA
   T  P  F  P  W  P  S  R  T  D  S  D  S  D  T  E  G  G  A  T

       130        140        150        160        170        180
CTGGTGGAGAGGCAGAGATGGACTTCCTGAGGAATTTATTCACCCAGACCCTGGGCCTGG
   G  G  E  A  E  M  D  F  L  R  N  L  F  T  Q  T  L  G  L  G

       190        200        210        220        230        240
GTTCCCAAAAGGAGCGTCTTCTAGACGAGCTGACCCTCGAAGGAGTGACACGCTACATGC
   S  Q  K  E  R  L  L  D  E  L  T  L  E  G  V  T  R  Y  M  Q

       250        260        270        280        290        300
AGAGCGAGCGCTGCCGCAAGGTCATCTGTTTGGTGGGAGCCGGAATCTCCACGTCCGCGG
   S  E  R  C  R  K  V  I  C  L  V  G  A  G  I  S  T  S  A  G

       310        320        330        340        350        360
GTATCCCTGACTTCCGCTCCCCGTCCACTGGCCTCTATGCAAACCTGGAGAAGTACCACC
   I  P  D  F  R  S  P  S  T  G  L  Y  A  N  L  E  K  Y  H  L

       370        380        390        400        410        420
TTCCTTACCCAGAGGCCATCTTTGAGATCAGCTACTTCAAGAAACATCCGGAACCCTTCT
   P  Y  P  E  A  I  F  E  I  S  Y  F  K  K  H  P  E  P  F  F

       430        440        450        460        470        480
TTGCCCTTGCCAAGGAGCTCTATCCCGGGCAGTTCAAGCCAACCATCTGCCACTACTTCA
   A  L  A  K  E  L  Y  P  G  Q  F  K  P  T  I  C  H  Y  F  I

       490        500        510        520        530        540
TCCGCCTGCTGAAGGAGAAGGGGCTGCTGCTGCGCTGCTACACGCAGAACATAGACACGC
   R  L  L  K  E  K  G  L  L  L  R  C  Y  T  Q  N  I  D  T  L

       550        560        570        580        590        600
TGGAACGAGTGGCGGGGCTGGAGCCCCAGGACCTGGTGGAGGCCCACGGCACCTTCTACA
   E  R  V  A  G  L  E  P  Q  D  L  V  E  A  H  G  T  F  Y  T

       610        620        630        640        650        660
CATCACACTGTGTCAACACCTCCTGCAGAAAAGAATACACGATGGGCTGGATGAAAGAGA
   S  H  C  V  N  T  S  C  R  K  E  Y  T  M  G  W  M  K  E  K

       670        680        690        700
AGATTTCTCAGAAGCAACTCCCAGGTGTGAGCAGTGTCA
   I  S  Q  K  Q  L  P  G  V  S  S  V
```

Figure 22

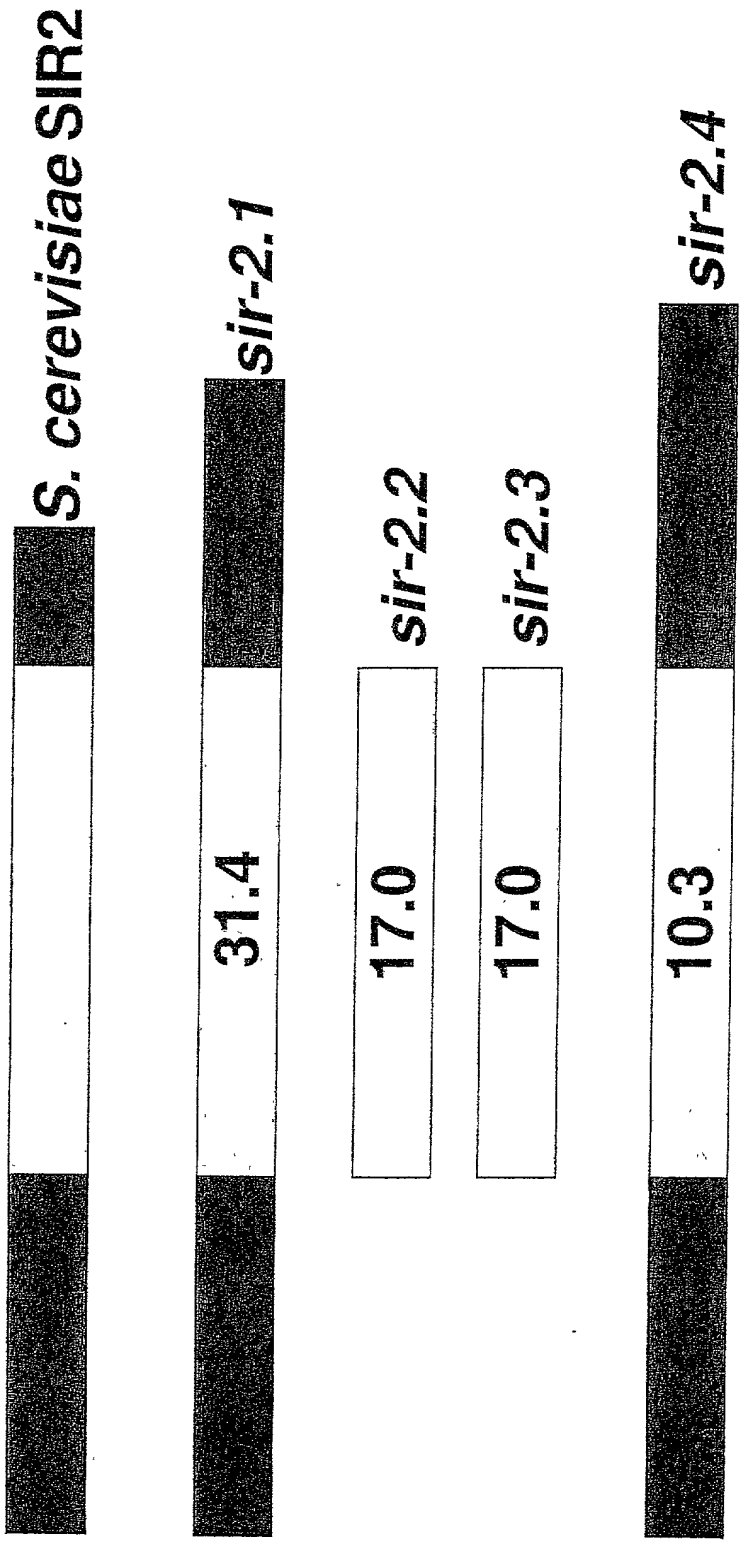

Figure 23

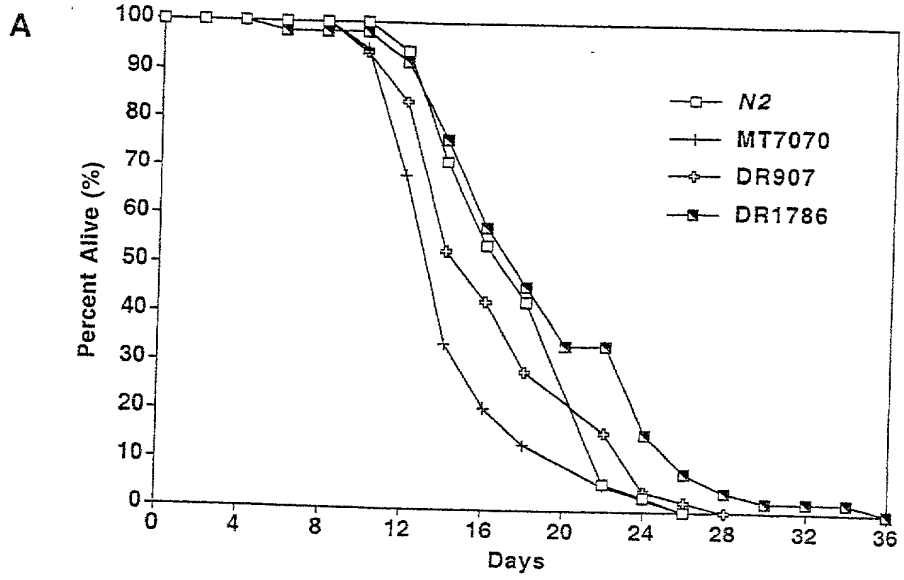

Figure 24A

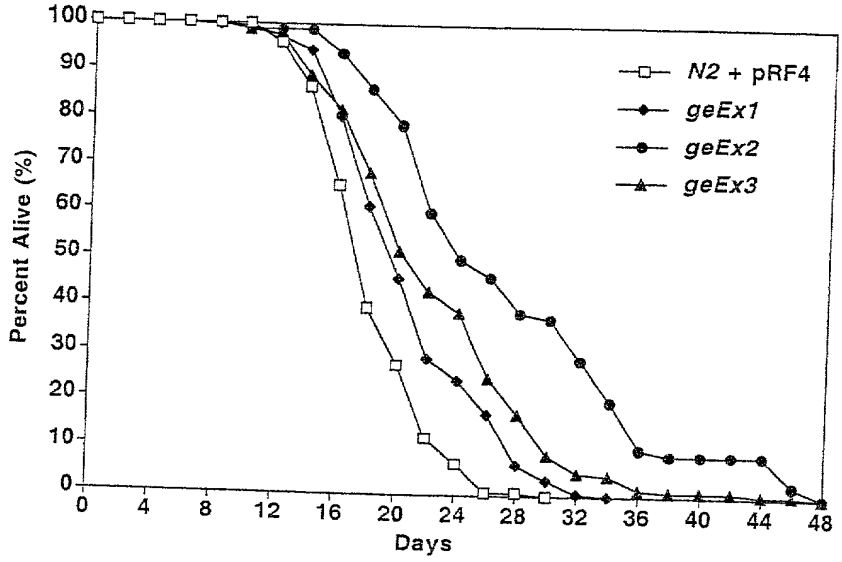

Figure 24B

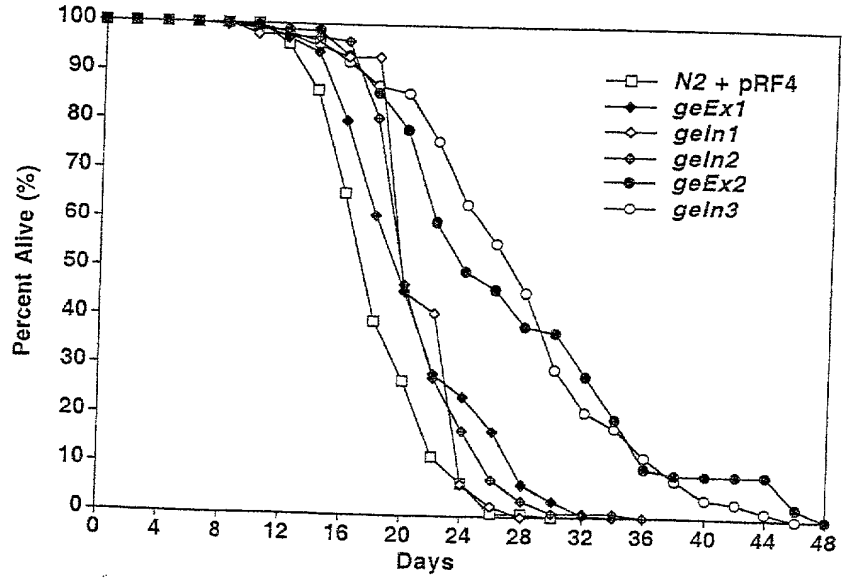

Figure 24C

A

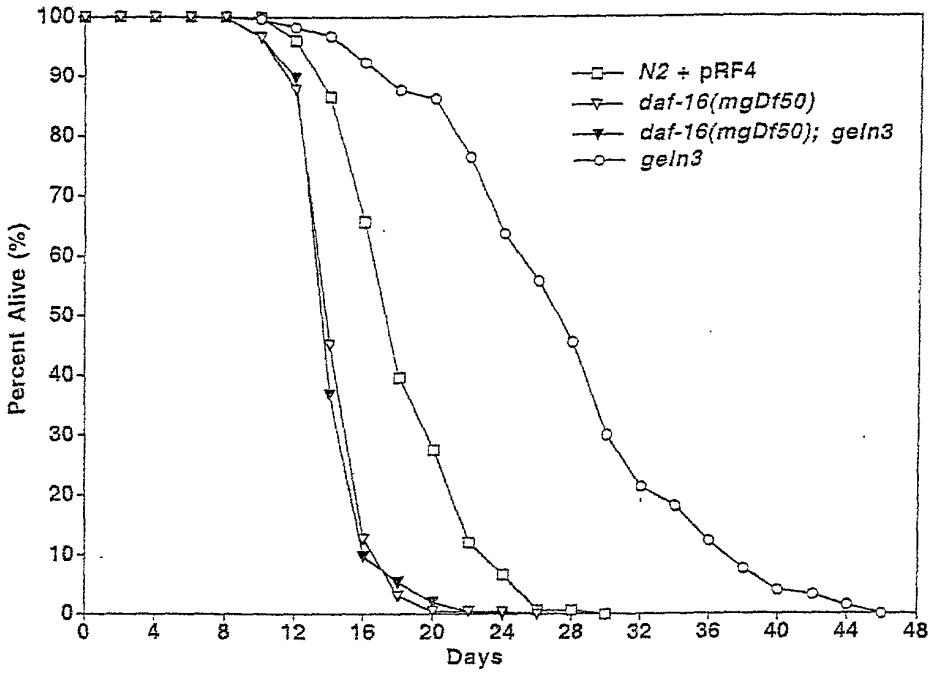

Figure 25A

B

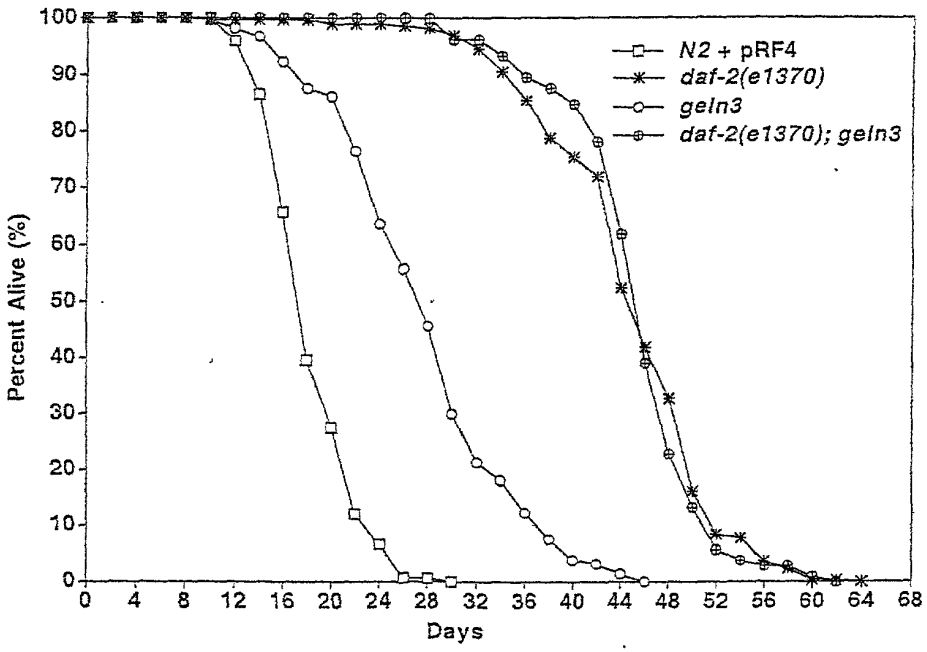

Figure 25B